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CHILD HEALTH SERVICES AND PEDIATRIC EDUCATION

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INTRODUCTION

The Study of Child Health Services and Pediatric Education has been reported in summary for the country as a whole[1] and is being reported in more detail for the individual states.[2] To summarize a summary approaches a reductio ad absurdum. But now that this momentous Study is not only completed but published, it is timely to point to a few of its most conspicuous highlights.

With the permission of the Commonwealth Fund, to whom we are indebted for publication of the report, we have reproduced below the final chapter of the report itself. These few pages are in the nature of a few drops of juice squeezed out of the fruits of our labors.

The full published report has been boiled down as much as has seemed consistent with an undertaking of this magnitude. In a first volume is to be found a general summary of child health services and pediatric education with a number of charts illustrating some of the most important findings. We have purposely avoided over-weighting this volume with heavy statistical tabulations. For those who are interested in more detail and a further analysis of the data, a second volume has been prepared containing methodology, definitions, comprehensive tabulated data, and the basic schedules used in collecting the desired information. So now, in two volumes, the report is available, prepared both for those who have general interest and for those who have more particular concern with the health of children and the training of the doctors responsible for their care.—*John P. Hubbard, M.D.*

GENERAL SUMMARY

WITH this Study completed and an array of facts spread out before us, it should again be emphasized that the collecting of this information was undertaken not as an end in itself, but as a means toward an end: the improvement of child health. The American temperament has a peculiar fondness for facts, surveys, and more surveys. Some surveys lead to sound planning; others, stripped of their guise, appear as substitutes for action. The words addressed to the National Health Assembly at one of its

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concluding sessions apply equally well here: "In some of the fields your sections have covered you will, of course, want to go out and gather more facts. Rightly! But in other cases I am sure that you have enough facts to spell out the answers: and in still other cases I bet you know the answers already and your next step is to do something about them."[3]

To do something about the facts has not been a function of the study committee. As stated in the introduction, this report attempts to answer the question "what is." The more important and far more difficult question, "what to do about it," is already being given serious consideration by a duly appointed committee of the Academy designated as the Committee for Improvement of Child Health. Also, in the individual states, state chairmen and committees are studying the data and making recommendations based on knowledge of local conditions.

Although recommendations do not form a part of this report, it would be a mistake not to review the findings in their broad perspective and in an objective manner present some generalizations from which action programs may profitably be developed.

Perhaps the most important fact, though not new or unsuspected, is the clear relation which is shown between services and the training of those who are giving the services. In the last analysis, good medical care for children depends not so much on the physical facilities of the hospitals or the expansion of health services, as upon the judgment and skill of individual physicians. This skill is the result of training and experience. It was this very fact which at the outset prompted us to couple with a study of child health services a study of pediatric education.

We have shown that three fourths of the private medical care of children is in the hands of general practitioners. Not only do general practitioners take care of most of the sick children, but they, as a group, do most of the well-child supervision.

The present system of medical education is poorly adapted to train a physician for a general practice so largely concerned with the care of children. Of the total hours which medical schools allot to pediatrics, certain schools provide over 300 hours in clinical clerkship in pediatrics. Others provide less than 50, which means that some students are graduated having received less than 50 hours of actual contact with child patients during their pediatric course.

One third of the children seen daily by the general practitioner and over half of the daily practice of the pediatrician come under the heading of health supervision. In view of the importance of health supervision of well children and the large place it occupies in the physician's daily schedule, the teaching of normal growth and development or the preventive aspects of child care is obviously inadequate.

Experience with patients during a period of internship or residency is invaluable in the preparation for practice. Such experience provides an opportunity to work under faculty supervision and to apply the knowledge gained during medical school years. Yet we have seen that nearly half of the general practitioners reported that they had had virtually no pediatric hospital training. Even today only two out of five physicians graduating from medical school have had any pediatric internship in hospitals approved for pediatric residency. It is not that these men had no desire for adequate instruction to prepare them to meet the problems of their day's work; rather it is an indictment of the system under which they have been trained. The eagerness of the general practitioner for post-graduate instruction and the efforts which he must make to fill

in the gaps in his course of training are evidence enough of the need for attention to this problem.

Even among the physicians who limit their practice to children, there are many of those not certified by the Board who have had comparatively little hospital work in pediatrics following graduation from medical school. Among these are a considerable number in the younger age groups, thus indicating that medical education is even now failing to provide adequate training to many who are becoming responsible for the health of the nation's children.

A large and important part of pediatric teaching is done by pediatricians who depend on their private practice for a livelihood and receive little or no remuneration for the time they give to teaching or the service they give to the hospitals. We have shown that over a third of the pediatric departments depend almost entirely upon the teaching done by these physicians who give their time and knowledge at virtually no cost to the institutions concerned.

Closely related to this situation is the gross inadequacy in the budgets of pediatric departments. Increasing attention is being directed to the crisis now confronting medical schools as a result of inadequate financial support. Pediatric departments reflect the gravity of the general situation. Half of the medical schools have pediatric budgets less than $25,000; 21 departments have budgets less than $10,000; and 11 less than $5,000 annually. Even these meager funds are obtained in large measure by dint of incessant work on the part of department heads and others whose time should be devoted to other duties.

The inadequate budgets of pediatric departments are only part of the problem. The cost of medical education to the student is such that, unless he belongs to the privileged few, he has not the means to continue his course long enough to acquire special knowledge. The expenses of the medical student, including tuition, are about $2,000 a year for a period of four years. During his hospital internship he usually receives little or no remuneration. By the time a physician is undergoing his hospital training, he is in his mid- and often late twenties, perhaps married and with a family. It is not surprising, therefore, that he may have to cut short his hospital work or that, if he has persevered through long specialist training, he may choose to settle in an urban community where income from practice is relatively high and where he may make up for his heavy expenses and late start.

The inadequacy of financial support for pediatric education stands in sharp contrast to the funds available for medical services. The large annual appropriations made available by Congress for maternal and child hygiene and the large sums raised from the public for care of children with special illnesses are many times more than the total annual budget of all medical schools for the purpose of training physicians in the medical care and health supervision of children. These wide differences should be considered in relation to the fact that all too often programs for child care are limited in scope and effectiveness by lack of well trained physicians.

Another broad generalization is inescapable. Children in outlying areas far removed from the medical centers usually found in the metropolitan areas do not receive the full benefits of modern medical care. Within few fields of human endeavor has such remarkable progress been made within the last generation as in medical science. New diagnostic technics and new life-saving drugs have increased the opportunities for

health and length of life. Never before has the infant mortality of the United States been lower or childhood disease more under control. Medical centers have increased in number and have widened the area of their services. Yet there is a time lag, and a serious one, between the newer knowledge of the medical center and its application to those living in places from which the medical center cannot be readily reached. For all the aspects of health services which fell within the scope of this study, deficiencies appeared in those counties which we have classified as isolated. And it must not be assumed that these isolated counties are all wide-open spaces sparsely populated—13,000,000 children, one third of the total child population, live in these counties.

One might expect to find in remote areas a conspicuous deficiency in respect to specialist care, clinic care, and the highly skilled diagnostic and therapeutic services. Many categories of specialist care do not represent an emergency, hence it is not essential to have specialists always on the spot. With the ease of modern travel, the child may be brought to the specialist or the specialist to the child even though the distances are great. A more serious deficiency exists in the distribution and services of the general practitioner. In isolated rural counties there were only one third as many general practitioners for the same number of children as in greater metropolitan counties. Not only do these physicians in remote areas have greater distances to travel and more children to care for during the course of a day, but also they are an older group who, although they undoubtedly have had wide experience, had less training before starting practice.

The need for increased hospital facilities throughout the country, especially in remote areas, has been recognized and is now being met under provisions of the Hospital Survey and Construction Act (the Hill-Burton program). Again, however, it may be pointed out that only in so far as well trained physicians are available to staff these hospitals will a better distribution of medical care be effected.

We have also shown that community health services, although they have increased tremendously in recent years under the auspices of official and voluntary agencies, still cover only a part of the need. In the isolated and remote areas where service from private practice and hospital clinics is comparatively low, there these community services are also low and fail to fill the gap.

Thus there are certain outstanding facts which emerge from the Study and which indicate quite clearly the steps that may be taken on the road to better health for children. First and foremost is the need for more physicians who are well trained in the care of children. This need must be met before other health measures can be effected. This need can be met only by strengthening pediatric education in medical schools and hospitals, for undergraduates and graduates, for general practitioners and specialists.

It is equally clear that the same high quality of medical care which exists in and near the medical centers must be made available in the remote and rural areas far removed from such centers. Inherent in medical schools is a unique potential for rendering services over and above the actual training of physicians. The very nature of medical training by the preceptor method, whereby interns and residents care for patients under the tutelage of able specialists, provides direct medical service of high caliber to people in surrounding communities. The findings of the Study point almost inevitably to decentralization and regional planning in order to extend the influence of medical teaching centers into the areas where deficiencies have been shown to exist.

Many agencies and organizations, both within and without the medical profession, are now actively concerned with these problems. Insofar as this Study has supplied information useful for constructive planning it will have accomplished its purpose of serving as a step toward better and more evenly distributed health for all children.

References

1. Child Health Services and Pediatric Education, By the Committee for the Study of Child Health Services of the American Academy of Pediatrics, with the cooperation of the U. S. Public Health Service and the U. S. Children's Bureau, The Commonwealth Fund, 41 East 57th Street, New York, N.Y., 1949, 296 pps., $3.50. (Note: The report is in two volumes. Volume I is a general summary of child health services and pediatric education; Volume II is a compilation of full and detailed statistical tabulations.)
2. For a list of state chairmen under whose auspices the individual state reports are being published, see op. cit., Volume II.
3. Hubbard, J. P., Pennell, M. Y., and Britten, R. H., Health services for the rural child, J.A.M.A. **137**:337, 1948.

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THERAPY AND PROGNOSIS OF FIBROCYSTIC DISEASE OF THE PANCREAS

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IN THE last ten years fibrocystic disease of the pancreas has become recognized as a not uncommon disease which is usually fatal in infancy or early childhood. During this period a considerable body of knowledge in regard to the disease has been accumulated by the efforts of many workers in this and other lands. Recognition of the clinical picture and development of a variety of pancreatic function tests have made possible the diagnosis of the disease during life. This in turn has enabled us to study the nutritional and respiratory phenomena and to attempt to apply these observations in therapy of the disease. The advent of penicillin and other new chemotherapeutic agents has altered the picture in this as in many other diseases.

In spite of all this progress, one of the most characteristic features of the disease remains to be explained, namely, the development of a persistent bronchitis. This is usually the cause of death, either directly as a suppurative bronchitis leading to bronchiectasis, atelectasis or other pulmonary complications or indirectly by way of cor pulmonalis. There are a number of curious features about this bronchitis. 1. Although it appears in the first half-year of life in most cases, it may not be present until some years have passed. 2. The bronchial secretion is viscous and may be abundant, accounting for the pertussis-like cough and the occasional instances of atelectasis. 3. Cultures taken early in the course of the disease grow Staph. aureus hemolyticus in nearly every case, usually in pure culture but sometimes temporarily associated with other organisms. A mixed flora is sometimes present in cases with a chronic bronchiectasis, with pyocyaneus as a common associate of the staphylococcus. 4. In many cases the infection seems mild as to toxic symptoms, and spreads to the lung parenchyma only in the terminal phase. Death is commonly by asphyxia due to pus filling the bronchi. Moreover, there is no apparent special susceptibility to staphylococcal infection of the skin or elsewhere than in the bronchi.

There are at present two schools of thought in regard to the relation between the pancreatic and bronchial lesions. The hypothesis first proposed was the concept that the lack of pancreatic secretion and consequent deficient digestion led to a deficiency of some substance essential for the normal functioning of the bronchi. The facts that vitamin A is poorly absorbed by these patients and that deficiency of vitamin A may lead to a change from ciliated to squamous epithelium in the bronchial mucosa suggested that vitamin A might be the specific substance.[1, 2] This remains an unproven possibility. The fact that intensive therapy with diet and supplementary vitamins does not appear to affect a well established bronchial lesion may be interpreted as evidence that such a

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lesion is irreversible and presents an example of locking the door after the horse was stolen. Since the absorption of vitamin A and presumably of other fat-soluble essential substances is greater when the dietary fat is low, it is logical to restrict dietary fat in general but with care to provide an abundance of foods known to contain a high concentration of these substances. The occasional late appearance of bronchial symptoms is explained as the result of the individual variation in the digestive efficiency of patients with the disease. Balance studies have shown wide variations in fecal loss of food, and it seems reasonable to suppose the patients with more efficient digestion have less tendency to a deficiency of specific food-stuffs. The obvious practical application of this viewpoint is to make every effort at early diagnosis in the hope that therapy will be early enough for effect in some cases at least.

The second hypothesis is that the bronchial lesion, like the pancreatic one, is on a congenital basis and is due to a hereditary defect in the nature of the mucus secreted by the bronchial glands.[3] The difficulty in the bronchi is therefore analogous to that in the pancreas, with occlusion of pathways by abnormally viscous material. The occasional late appearance of bronchial symptoms is interpreted as a late development of the abnormality of the bronchial secretion and, by analogy, a late development of the pancreatic lesion is considered possible. The tendency of patients to relapse after initial response to chemotherapy is interpreted as the inevitable result of the abnormality of the bronchial mucus. The obvious practical application of the second hypothesis is pessimism with respect to benefit from dietary therapy, since it cannot, according to this view, affect the inevitable pulmonary lesion, and since most patients will eat enough to sufficiently compensate for fecal loss and thus to produce gain in weight as long as there is no severe infection. The rational therapeutic approach on the basis of this hypothesis is therefore to provide chemotherapy as indicated, and to recommend a good normal diet as desired.

Neither of these hypotheses rests on final and convincing proof, yet we are forced to act on one or the other in the course of treating our patients. It has seemed worthwhile to scrutinize the data obtained at the Babies Hospital during the last ten years for evidence which would bear on the question.

A fact may be pointed out which may not be evident to those who have not studied the pathologic lesions in the bronchi in these cases. The congenital theory does not rest on morphologic proof. In cases of meconium ileus dying in the neonatal period the bronchi appear normal or show only the effect of aspiration of vomitus. In older cases the mucus secreted by the bronchial glands is abundant and viscous but does not differ morphologically from that seen occasionally in other types of cases, notably in patients dying during an attack of asthma. This mucus does not resemble morphologically the contents of the pancreatic ducts and acini in cases of fibrocystic disease. The contents of the pancreatic cysts is eosinophilic and tends to have a pattern of concentric rings in hyaline-like material. Occasionally in older cases the cysts are large enough to see under a dissecting microscope and their contents can sometimes be seen as hard, rounded, pale amber pellets. On the other hand the bronchial mucus is gray and viscous, and on microscopic section it is basophilic and streaked and can be seen to extend from the ducts of the mucous glands in the same way that it may do in cases of asthma. There may or may not be a specific functional abnormality of the bronchial mucus in fibrocystic disease, but the morphologic evidence for such an abnormality is weak.

A second point should be made in regard to the character of the mucus in fibrocystic

disease. If in the future the mucus is shown to be abnormal in some specific manner, the questions of a congenital or nutritional basis for that abnormality would remain to be demonstrated. Some functional if not morphologic change in the bronchi may be expected to precede the bronchitis in either case.

It is quite possible that the primary difficulty does not lie in the nature of the mucus. An attractive alternative suggestion is the loss of cilia of the bronchial mucosa. Until

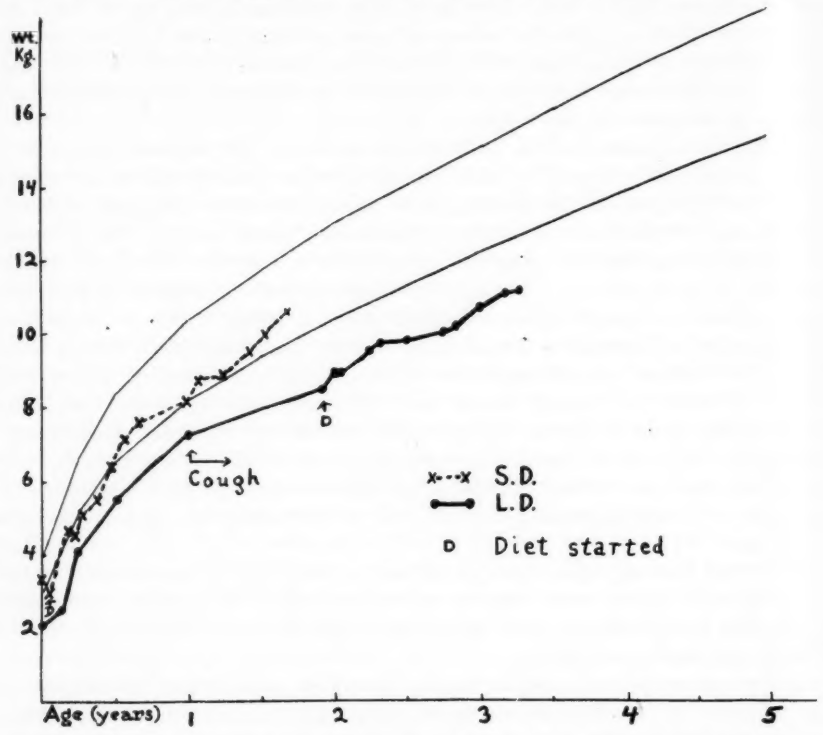

FIG. 1. Comparison of weight curves of two sisters. One of them, L. D., was undiagnosed until soon after onset of her respiratory infection at 12 months, and the other, S. D., was placed on dietary therapy at 2 months of age and has remained free of respiratory infection.

means are devised for testing these various possibilities the question of the mechanism of the bronchial changes should be considered open.

For some years the assumption has been that the nutritional hypothesis is correct. The hypothetic specific deficiency responsible for the pulmonary lesion has not been demonstrated. It may or may not be vitamin A deficiency. Until proof of such a specific deficiency is at hand the evidence for the nutritional hypothesis must be indirect. Moreover, therapy based on such an hypothesis must consist of general rather than specific measures.

The evidence to be presented here consists of three types of data in support of the nutritional hypothesis: first, on the thesis that nutrition is adequate in the absence of infection; second, evidence that general dietary measures affect the absorption of specific substances; and third, an analysis of the status of patients of this series as of July 1948

for the purpose of discovering the value of dietary therapy, chemotherapy and early diagnosis.

First, in regard to the question whether nutrition is adequate in the absence of infection. No evidence for or against this is provided by the older infants and children of this series since all have been on dietary therapy except a few who have not followed advice, and these all had chronic bronchitis when first seen. It follows that all who are of normal weight for their age have been on dietary therapy. Evidence is provided, however, by the response to dietary therapy of young infants who were placed on diet prior

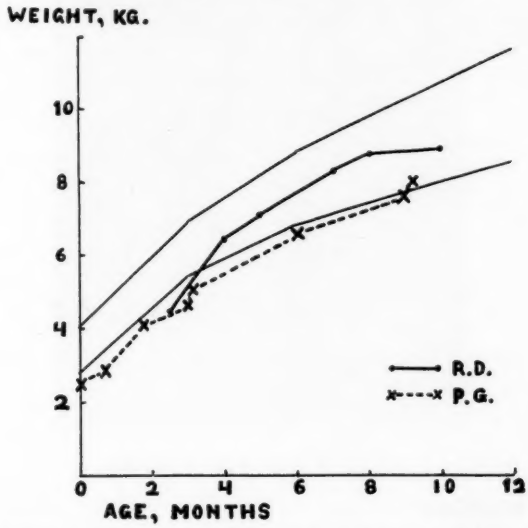

FIG. 2. Weight curves of two infants diagnosed before age of 2½ months because of similar disease in older sibling. R. D. has remained without infection. P. G. had slight cough when first seen which has persisted but not progressed.

to the onset of a respiratory infection. In the majority of cases of fibrocystic diseases a marked weight lag occurs in the first two months, presumably because other organs of digestion are not sufficiently mature to compensate for lack of pancreatic function. A formula which was originally devised for infants surviving operation for meconium ileus has proved beneficial in other cases in early infancy.[4] This, in powdered form, consists of protein milk 50 parts, amino acids (casein hydrolysate) 5 parts, banana powder 20 parts and glucose 20 parts.* This, together with supplements of vitamin A, D and B complex and pancreatin has been used in nearly all infants under six months of age for the past few years. Response to this regime is shown in the accompanying weight curves. The benefit of early dietary control is especially clear in the case of two sisters, L. D. and S. D. (Fig. 1), one of whom had a slow gain for a long period before her respiratory infection, and the other, diagnosed prior to infection because of the diagnosis on her older sister, is of normal weight and has remained without infection.

Two other weight curves are shown (Fig. 2), both of infants in whom the diagnosis

* Prepared by Mead Johnson Company under the name of special formula #235.

FIG. 3. R. D. at age of 9 months.

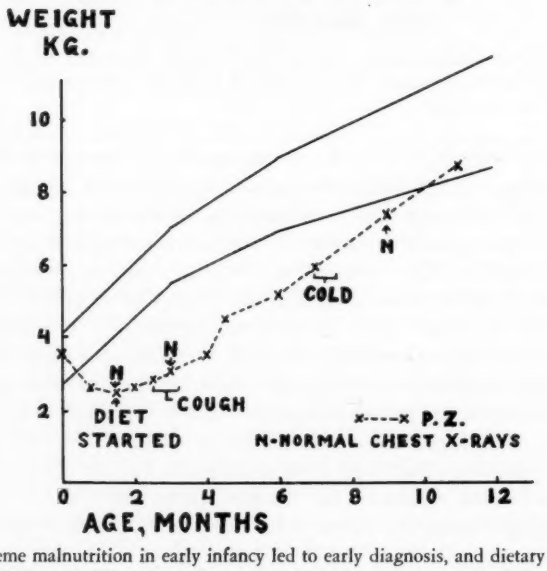

FIG. 4. P. Z. Extreme malnutrition in early infancy led to early diagnosis, and dietary therapy preceded initial cough. There is no chronic cough and lungs have remained clear.

was made early because of disease in a sibling. R. D. (Fig. 3) has remained without cough and P. G. had a slight cough when first seen which has persisted. The diagnosis was made in P. Z. (Fig. 4) because of extreme malnutrition. Dietary therapy preceded his first cough; he has had two colds, with lungs normal to roentgenogram thereafter.

Evidence that general dietary measures affect the absorption of specific substances is provided by a comparison of the vitamin A absorption curve after ingestion of 7,000 units of vitamin A per kilogram of body weight in the form of oleum percomorphum done while the patient was on a normal ward diet with whole milk as compared with a

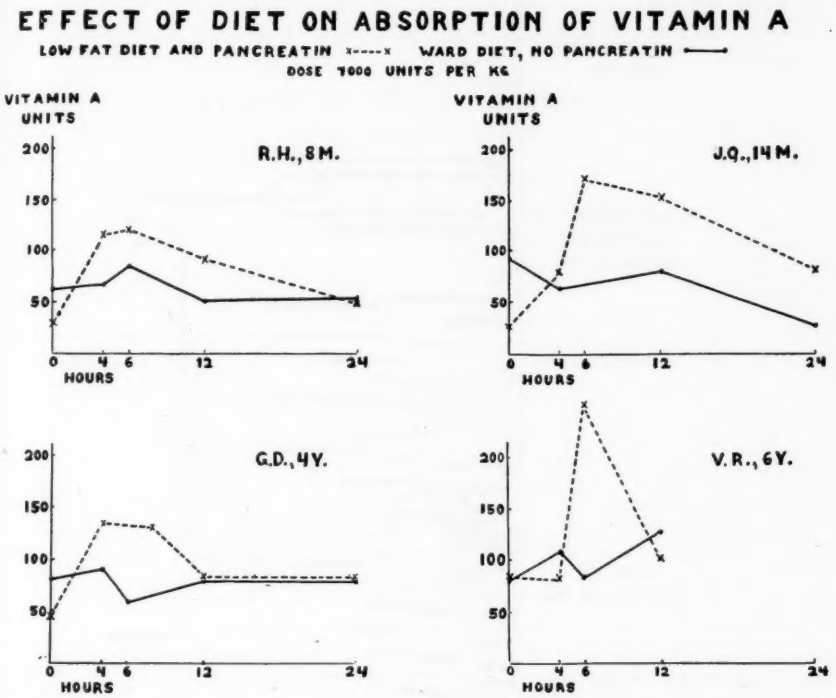

FIG. 5

curve done while the patient was receiving a low fat diet with skim milk and pancreatin (Fig. 5). In the latter the curve shows fair to good absorption. It is reasonable to suppose that at least some other fat-soluble essential substance may behave in a similar manner.

The third type of evidence consists of clinical results of acting on the nutritional hypothesis. Since 1939, enough experience has been accumulated to warrant an attempt at evaluation of the results of the policy of early diagnosis followed by dietary therapy with chemotherapy as indicated. The advent of penicillin has added a new factor, and has made it necessary to consider separately the cases of the pre-penicillin and the penicillin eras. Fig. 6 shows a comparison in the length of survival of the cases of the series prior to 1939, the year which marks the first clinically diagnosed case; between 1939

and July 1944, the years during which diagnosis and dietary therapy were available, and after July 1944 when penicillin was also available. In the first group the majority died of respiratory infection after a few days or weeks of hospitalization. In the second group,

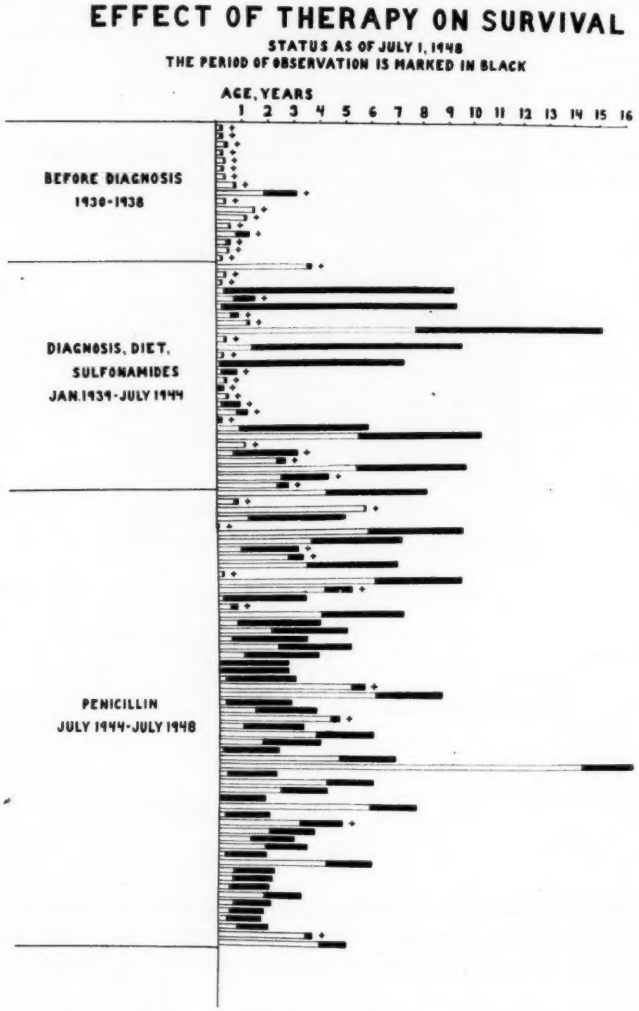
EFFECT OF THERAPY ON SURVIVAL
STATUS AS OF JULY 1, 1948
THE PERIOD OF OBSERVATION IS MARKED IN BLACK
AGE, YEARS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
BEFORE DIAGNOSIS
1930-1938
DIAGNOSIS, DIET,
SULFONAMIDES
JAN. 1939-JULY 1944
PENICILLIN
JULY 1944-JULY 1948

FIG. 6

numbering 28, eight are still living, having survived the first years without benefit of penicillin. Since 1944, 79 cases have been added to our series. The majority have responded to the initial course of chemotherapy, and many of those who were treated before the infection had become chronic have continued without recurrence of the infection. All

have received dietary therapy essentially similar to that previously described except that for the past three years most of the infants under six months of age have received formula #235. A summary of the status of all patients seen between 1939 and 1948 is presented (Fig. 7).

In Tables I and II the status of the pre-penicillin era group as of July 1944 is compared with the status of the penicillin era cases as of July 1948, to compensate for the difference in time of observation. It is clear that penicillin has had more effect on the survival of the group in which a chronic cough was present before the age of six months than of the group with later onset of cough. In many instances this may be attributed to the presence of a long established bronchial infection in the late group by the time diagnosis is made. The benefit of chemotherapy is often temporary in these cases.

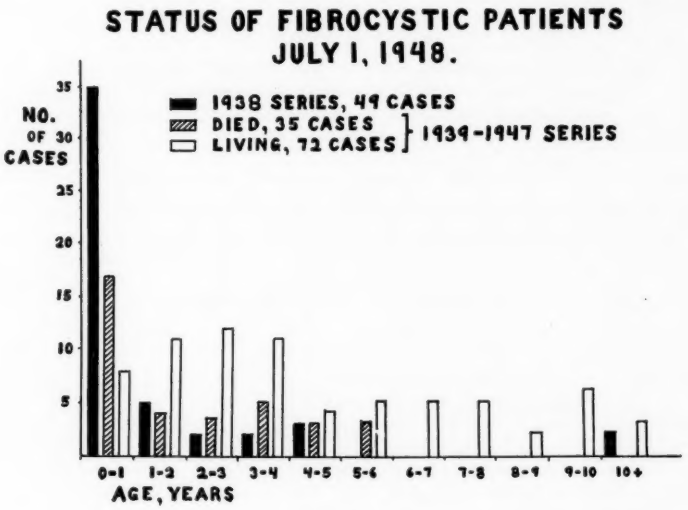

FIG. 7

Part of the improvement in the survival rate since 1944 can be attributed to greater awareness of the disease, early diagnosis and also, it is believed, dietary therapy. In not a few the diagnosis has been made prior to the first observed cough, and in some the initial cough has appeared within a few days or weeks of commencing dietary therapy. Penicillin has been available as needed to all patients seen since July 1944. Table III presents analysis of the status as of July 1, 1948 of 76 of the cases seen since 1944 with regard to the time relation between the first observed cough and the start of dietary therapy. It will be seen that of the 76 cases, 21 have no cough; most of these also have no roentgen evidence of pulmonary infection and the majority of them received dietary therapy within two months of the initial cough. The patients in "good" condition have a cough but are gaining weight and are normal in activity or nearly so. Those in "poor" condition have a cough, are not gaining weight and are considered to have a poor prognosis.

Comparison of the number of cases with no cough with all the others in relation to the

TABLE I

EFFECT OF ADVENT OF PENICILLIN ON SURVIVAL OF EARLY AND LATE CASES

	Onset of cough	No. of cases	Living, Age, Years			Died, Age, Years		
			<1	1–5	5+	<1	1–5	5+
Cases 1–28	<6 m	19	0	1	3	10	5	0
as of July 1944	>6 m	9	0	2	5	0	2	0
Total		28	0	3	8	10	7	0
Cases 29–107	<6 m	45	6	21	11	5	2	0
as of July 1948	>6 m	28	1	11	10	0	2	4
	No cough	3	1		1	1	0	0
Total		76	8	32	22	6	4	4

TABLE II

EFFECT OF ADVENT OF PENICILLIN ON SURVIVAL OF EARLY AND LATE CASES

Onset of Cough	Series	No. of Cases	Per Cent Living at Age, Years	
			1	5
Before 6 mos.	Cases 1–28, as of July 1944	19	21%	14%
	Cases 29–107, as of July 1948	45	71%	24%
After 6 mos.	Cases 1–28, as of July 1944	9	77%	19%
	Cases 29–107, as of July 1948	28	79%	36%

TABLE III

EFFECT OF EARLY DIAGNOSIS AND DIET; CASES SINCE JULY 1944. CASES 29–107

Interval, start diet to cough	Status as of July 1, 1948			
	No cough	Good	Poor	Died
No cough	2	0	0	(1)*
Diet preceded cough	6	1	1	1
0–2 m	8	5	4	2
2–6 m	4	9	1	1
Over 6 m	1	11	9	7
No diet	0	0	0	2
Total	21	26	15	14

* Died with diarrhea at 1 month; lungs normal. Not on diet.

TABLE IV

CHI-SQUARE COMPARISON OF NUMBER OF CASES WITHOUT COUGH WITH ALL OTHERS IN RELATION TO INTERVAL BETWEEN COUGH AND START OF DIETARY THERAPY. 1944–1948 SERIES.

	Interval cough to diet		
	<2 m.	>2 m.	
No cough	16	5	21
Others	15	40	55
Total	31	45	76
$\chi^2 = 15.0$		P<.001	

TABLE V

PATIENTS WITHOUT KNOWN RESPIRATORY INFECTION AS OF JULY 1, 1948
Diagnosis confirmed by duodenal drainage and demonstration of steatorrhoea
M.I.—Meconium Ileus; Cl.—Clinical Picture; F.H.—Family History

Case	Means of Dx	Time Diet to Cough	Start Diet, Age	Onset Cough, Age	Penicillin at	Roentgenogram Neg. at	Present Age
86. J.M.	M.I.	No cough	1 m	None	0	5 m	1 y
85. A.R.	Cl.		6 m	None	0	4 y	5 y
89. P.Z.	Cl.	Diet preceded	6 w	7 m	0	9 m	11 m
69. J.T.	F.H.	cough	3½ m	4 m	4 m	4 m	2 y
50. C.F.	M.I.		1 m	2 5–12 y	1 m; 2½ y	2½ y	2 9–12 y
60. N.W.	Cl.		1 10–12 y	2 1–12 y	2 4–12 y	4 y	4 y
47. R.F.	Cl.		5 m	6 m	0	2 2–12 y	4½ y
59. A.P.	Cl.		1 3–12 y	3 y	4 6–12 y	4 7–12 y	6 11–12 y
96. R.D.	F.H.	0–2 m after	2½ m	2 m	0	2½ m	10 m
81. B.O.	M.I.	cough	5 m	4 m	4 m	1 4–12 y	1 9–12 y
74. S.D.	F.H.		2 m	7 w	3½ m	1 7–12 y	1 10–12 y
76. J.R.	Cl.		2 m	1 m	7 m	1 8–12 y	2 2–12 y
61. H.B.	Cl.		3 m	2 m	8 m	2 4–12 y	2 4–12 y
42. B.N.	F.H.		1 m	1 m	3 m	3 3–12 y	3 6–12 y
49. R.H.	Cl.		10 m	10 m	0	3 9–12 y	3 11–12 y
62. H.B.	Cl.		2 m	2½ w	0	4 10–12 y	6 11–12 y
13. M.O.	F.H.		6 w	6 w	0	7 y	7 3–12 y
103. K.B.	Cl.	2–6 m after	6 m	3½ m	2½ m	5 m	8 m
98. A.V.	Cl.	cough	9 m	5 w	6 w; 1 2–12 y	1 6–12 y	1 7–12 y
35. A.O.	Cl.		3 8–12 y	3 y	0	3 9–12 y	6 2–12 y
92. E.G.	Cl.		10 m	"Infancy"	0	4 3–12 y	5 y
34. J.H.	Cl.	Over 6 m after cough	5 11–12 y	1½ y	0	9 6–12 y	9 6–12 y

institution of dietary therapy within two months of the first cough gives a χ^2 of 15.0 and a P. < .001 (Table IV).

No series of cases of fibrocystic disease without respiratory infection has been previously reported and it is of interest to present a few details of these patients (Table V). Early diagnosis was made by three means: first, by alertness in suspecting the disease, and

frequent inclusion of pancreatic fibrosis in differential diagnosis with elimination by laboratory means of those cases given an erroneous provisional diagnosis; second, by searching the families of proven cases for older or younger siblings with the disease; and finally, by making a presumptive diagnosis and applying dietary therapy early in the operated cases of meconium ileus. The date of the most recent roentgen examination is given. Questionable mild bronchial thickening was reported in two cases without symptoms and the lungs were considered normal in the remainder.

Of the 22 cases, 11 have never received penicillin, nine received one course of penicillin therapy near the onset of respiratory symptoms and have had no recurrence of symptoms, while two have required a second course but subsequently had normal roentgenograms and are without symptoms.

Analysis of the 14 fatal cases shows that they fall into three categories. Two patients with onset of symptoms in early infancy died undiagnosed within a week of admission. Three patients with early diagnosis gave no response to penicillin therapy and were found to harbor a resistant organism. The remaining nine cases had lung infection of long standing which responded initially to penicillin therapy but on subsequent recurrence failed to respond. Most of the patients in "poor" condition are similar to these last and may be expected to join them.

The majority of cases considered in "good" condition are older infants who have responded to penicillin therapy but retain more or less evidence of continued infection. Some have had no recurrence of infection for several years but further observation is needed.

Discussion

The evidence presented here is in favor of a nutritional hypothesis of the etiology of the respiratory infection in fibrocystic disease of the pancreas. This evidence is based primarily on the number of patients who received early dietary therapy and who have remained free from important bronchial infections. The question of the etiology of fibrocystic disease of the pancreas will not be settled until there is proof either of a specific deficiency and the mechanisms by which it operates or of some congenital abnormality of the bronchi. In the meanwhile, there is sufficient evidence for the nutritional hypothesis to lead to practical application of it. Since the hypothetical specific deficiency is unknown, dietary therapy must depend on general knowledge of digestive function in pancreatic deficiency. In view of the wide variations in the natural history of the disease, occasional failures may be attributed to incomplete knowledge and to human failures in carrying out the diets. The failure of response of patients with pulmonary lesions of long standing or with infection by organisms resistant to available chemotherapeutic agents is to be expected. In the long run the chief benefit of penicillin will probably be in the prompt control of early stages of infection.

Summary and Conclusions

The etiology of the respiratory lesion in fibrocystic disease of the pancreas is discussed with a summary of the congenital and nutritional hypotheses.

There is no morphologic evidence that a specific congenital abnormality exists in the bronchi or in their secretion. The microscopic appearance of the mucus does not resemble that of the contents of the pancreatic ducts but does resemble the mucus seen in some other clinical conditions, notably asthma. A physiologic congenital abnormality of the bronchi is possible but unproven.

Evidence is presented that dietary therapy improves the growth curves of infants diagnosed and treated prior to infection.

The absorption of vitamin A, and presumably of other fat-soluble specific substances, is affected by diet.

Twenty-two cases of fibrocystic disease without clinical evidence of respiratory infection are presented. Twenty-one of these were first seen after penicillin became available but only 11 have received it. The majority of the 22 patients were started on dietary therapy before a cough had been present for as long as two months. This record is presented as evidence in favor of a nutritional factor in the etiology of the respiratory infection.

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SPANISH ABSTRACT

Terapia y Prognosis de la Enfermedad Fibrocística del Pancreas

Se habla de la etiología de la lesión respiratoria en la enfermedad fibrocística del pancreas con un sumario de la hipótesis congénita y nutritiva.

No hay prueba morfológica de que existe una anormalidad congénita en los bronquios y en su secreción. La apariencia microscópica del moco no se parece a la de los conductos pancreáticos; pero si se parece a la que se ve en el asma. Una anormalidad congénita fisiológica de los bronquios es posible; pero sin prueba.

Se ha presentado prueba de que la terapia dietética mejora las curvas de crecimiento de niños diagnosticados y tratados antes de la infección.

La absorción de vitamina A y presumiblemente la de otras sustancias específicas capaces de disolver grasa queda afectada por la dieta.

Se presentaron 22 casos de enfermedad fibrocística sin prueba clínica de infección respiratoria. Vientiuno de éstos se vieron por la primera vez cuando se podía obtener la penicilina, pero solamente once la recibieron. La mayoría principió con terapia dietética antes de que se presentara una tos—hasta dos meses. Esta información se presenta como prueba en favor de un factor nutritivo en la etiología de la infección respiratoria.

622 West 168th St.

RENAL CLEARANCES OF SODIUM PENICILLIN G, PROCAINE PENICILLIN G, AND INULIN IN INFANTS AND CHILDREN

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PROCAINE penicillin has been reported to provide a highly effective means of prolonging the action of penicillin, as evidenced by the height and duration of drug concentrations in the blood following a single intramuscular injection.[1-3] The explanation of its effectiveness in achieving prolonged drug action has been presumed to lie in the fact that it is relatively insoluble and hence slowly absorbed from the site of injection.

In reviewing the few available reports on procaine penicillin, however, it has been striking to note not only that measurable concentrations were present in the serum of adults for a prolonged period after a single dose, but that in many instances surprisingly high levels were recorded. For example, in samples of serum taken following intramuscular injection of 300,000 units, concentrations as high as 4 u./ml. were found in some subjects. In other instances, levels of 1 and 2 u./ml. were recorded in successive samples taken at three hour intervals in the same subject.[1,2]

The reported occurrence of unexpectedly high serum concentrations of penicillin in normal subjects might, of course, be explained by variations in dosage or by errors inherent in the bioassay technic. Nevertheless, these findings suggested the possibility that in addition to the primary factor of slow absorption, the renal clearance of procaine penicillin might be lower than that of the sodium salt, thereby acting as a secondary factor in prolonging the action of procaine penicillin.

Accordingly, a study has been made of the renal clearance of procaine penicillin G and sodium penicillin G, in an attempt to determine if reduction in renal excretion of procaine penicillin contributes to the prolonged action of this drug.

METHODS

Measurements were made of inulin clearances and of the clearances of either sodium penicillin G or procaine penicillin G in 10 children and four premature infants. In two of the children (KU and HE) clearances of both penicillin salts were measured in separate experiments on different days. The infants and children had no indications of kidney disease and the inulin clearances provided a check on the normality of their kidney function. Protocols for all subjects are included in Tables I and II. All observations were made in an air-conditioned metabolism unit in which the temperature and humidity were maintained at 26°C and 60%, respectively.

The clearance procedures and chemical methods have been described in detail.[4] Saline solutions of sodium and procaine penicillin G* were prepared in concentrations of 10,000 and 2500 u./ml.,

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* The penicillins were supplied by Charles Pfizer & Co., Inc., Brooklyn, N.Y.

TABLE I

PROTOCOLS AND DATA ON INULIN AND PENICILLIN CLEARANCES IN CHILDREN

Subject	Sex	Age yrs.	Wt. kg.	Ht. cm.	S.A. M^2	Range of Penicillin concentrations Units/ml. serum	Clearances ml./min.				
							Inulin		Penicillin		
							Actual	Corrected per 1.73 M^2	Actual	Corrected	
										per 1.73 M^2	$\frac{C_{PEN} \times 100}{C_{IN}}$
Sodium Penicillin G											
TA	M	11.3	37.8	150	1.29	2.50–0.81	92.9	120.8	239.2	311.0	257.5
PA	F	11.6	46.7	149	1.38	1.00–0.63	113.6	143.1	287.4	362.1	253.0
KU	F	8.5	33.2	134	1.10	0.75–0.63	85.3	133.8	607.6	953.9	712.9
HE	M	8.75	26.3	127.5	0.96	0.80–0.60	76.1	137.0	400.5	720.9	526.2
KUB	M	11.0	41.9	142	1.26	0.60–0.42	90.3	123.7	338.7	464.0	375.1
HEI	M	9.5	30.4	143	1.14	0.49–0.49	96.7	145.1	510.2	765.3	527.4
Mean							92.5	133.9	397.3	596.2	442.0
Procaine Penicillin G											
TR	F	7.0	29.1	136	1.07	0.63–0.38	77.2	125.1	340.7	551.9	441.3
CL	F	11.0	29.0	—	Est. 1.10	0.75–0.63	77.7	124.2	242.6	388.2	312.6
LY	F	2.75	13.2	94.5	0.58	0.20–0.49	31.3	93.3	173.9	518.2	555.4
BU	F	3.8	20.8	112	0.82	0.75–0.75	59.5	125.0	156.5	328.7	263.0
KUB	M	11.0	41.9	142	1.26	0.49–0.38	87.3	120.5	383.1	524.8	435.5
HEI	M	9.5	30.4	143	1.14	0.38–0.38	89.1	133.6	548.7	823.1	615.8
Mean							70.4	120.3	307.6	522.5	437.3

TABLE II

PROTOCOLS AND DATA ON INULIN AND PENICILLIN CLEARANCES IN PREMATURE INFANTS

Subject	Sex	Age days	Wt. gm.	Height cm.	S.A. M^2	Range of Penicillin Concentrations Units/ml. serum	Clearances ml./min.				
							Inulin		Penicillin		
							Actual	Corrected per 1.73 M^2	Actual	Corrected	
										per 1.73 M^2	$\frac{C_{PEN} \times 100}{C_{IN}}$
Sodium Penicillin G											
PI	F	8	2290	47	0.172	1.0–1.0	5.28	53.2	11.34	114.1	214.8
MA	F	4	2320	47	0.180	1.0–1.5	3.26	31.3	9.64	92.6	295.7
Procaine Penicillin G											
GR	F	6	2220	47.5	0.170	0.8–1.5	4.65	47.3	7.14	72.7	153.5
PE	F	7	2308	47	0.176	0.5–1.0	4.62	45.4	8.01	78.7	173.4

respectively. For both penicillin salts a priming dose of 500 u./kg. was found to give approximately 0.5 u./ml. of serum. The concentration of penicillin incorporated in the infusion fluid was calculated on the basis of expected serum level and clearance. Penicillin was determined by a method previously described,[8]

Results

Children

In Table I are shown the mean values for observations on the children. Each clearance value listed represents the mean of at least three clearance periods. The inulin and penicillin clearances are presented in Table I both as uncorrected values of UV/P, and as values corrected for surface area by the factor 1.73/surface area.* In addition, the penicillin clearances have been calculated as the clearance per 100 ml. inulin clearance.†

As may be seen from the data in Table I, no significant differences between the clearances of sodium penicillin G and procaine penicillin G were found. When corrected for differences in inulin clearances, the mean values for the two types of penicillin are practically identical. The wide variation in the penicillin clearances in contrast with the narrow range of values for the inulin clearances reflects the relative inaccuracy of the bioassay technic for penicillin. The mean value for the clearances of penicillin G corrected for surface area is lower than the values reported by Eagle and Newman,[7] but the wide spread of the data in both series makes it appear that the discrepancy is due to inaccuracy of the assay method rather than to other factors such as the younger age of our subjects. Inulin clearances measured simultaneously serve to show whether, per unit surface area, penicillin clearances in children of the age we observed may be expected to fall within the adult range. In this series of 10 children of both sexes, ranging in age from 2.75 to 11.6 years, and in weight from 13.2 to 46.7 kg., the mean value for inulin clearance was 126.6 ± 13.2 ml./min./1.73 M^2. This is well within the range of values published for adult subjects,[8] and the penicillin clearances corrected for surface area would be expected, therefore, to be within the adult range.

Premature Infants

There is adequate evidence that in young infants kidney functions are reduced even when calculated on the basis of clearance per unit surface area.[4] This incomplete physiologic development of kidney function should be considered in translating dosage of therapeutic agents from adults to young infants. It seemed of interest, therefore, to measure penicillin clearances in premature infants in order to determine the magnitude of the anticipated reduction in clearance in young infants, and the effect this might be expected to have on penicillin blood levels.

In Table II are listed the clearances determined in four premature infants. Again, each individual value represents the mean of three or more clearance periods. Although the relation of clearances in young infants to surface area, body weight, metabolic rate, age or other standard of reference has not been fully established for the purpose of comparison of the values with those of the children, the clearances of penicillin are given as uncorrected values and as corrected for surface area and for rate of glomerular filtration.

Comparison of the clearances of the two penicillin salts in the premature infants again shows that they do not differ significantly. There is, however, an appreciable reduction in the clearances of both penicillin salts in comparison with that of the children. The clearances of penicillin corrected for surface area are only 17% of the clearances of the children, and only 34% if corrected for body weight.

Comment

From the observations described, it may be concluded that the clearance of procaine penicillin G is the same as that of sodium penicillin G. Indeed, from the known pharmacologic behavior of procaine, one might expect procaine penicillin to be highly unstable *in vivo,* and it is therefore entirely possible that the clearances measured actually represent the clearances of another salt which is formed *in vivo* immediately after ad-

* The surface area of the children was obtained by using weight and height from the monogram of DuBois and DuBois.[6]

† In effect, this calculation indicates what the penicillin clearance would be if the inulin clearance were 100 ml./min., in the same fashion as correction for surface area indicates what the clearance would be if the surface area were 1.73 M^2. Although this calculation has no direct physiologic significance, it serves to correct the penicillin clearances in different subjects on the basis of an independently measured kidney function.

administration. Nevertheless, the data permit a fairly accurate estimation of the maximum possible time any given concentration of penicillin may be maintained in the blood following administration of a known amount. For example, at a constantly maintained serum level of 0.1 u./ml., the rate of excretion of procaine penicillin would be approximately 50 u./min./1.73 M^2. Consequently, under ideal conditions, a single dose of 300,000 units could maintain this level for as long as 100 hours. This would not obtain, however, if the level were above 0.1 u./ml. for any length of time. For example, if levels of 4 u./ml. were maintained continuously, 300,000 units would be completely excreted in 2½ hours. For a critical evaluation of data on maintenance of drug levels obtained with a particular preparation of penicillin, it is essential to consider the limits imposed by the rate of excretion. The observation of values which appear to fall outside these limits presumably indicates that absorption of the material has been irregular, that the dosage was inaccurate, or that significant errors in measurement have been made. In this regard, it should be stated that, although the measurement of penicillin in serum is subject to many inaccuracies, the percentage error in a series of determinations hardly appears sufficient to explain the discrepancies noted.

The degree of reduction in penicillin clearances in premature infants suggests that if penicillin is given to small infants in dosages proportionate to their surface area, and if the rate of absorption is approximately the same, the duration of drug concentrations in the blood should be six times as long as in children and adults. If given in dosages proportionate to their weight, the more common practice, levels should be maintained three times as long. These factors may be slightly lower due to a greater volume of distribution of penicillin in the body of the premature infant.

Summary and Conclusions

Reports of unexpectedly high serum concentrations of procaine penicillin G suggested the possibility that, in addition to the major factor of slow absorption, the renal clearance of procaine penicillin might be lower than that of the sodium salt.

Measurements of inulin clearances and clearances of either sodium penicillin G or procaine penicillin G in 10 children and four premature infants showed no significant difference between the clearances of the two penicillin salts. A reduced clearance of procaine penicillin, therefore, does not explain the apparent occurrence of unexpectedly high serum concentrations of penicillin in normal subjects.

Critical evaluation of data on the maintenance of drug levels with a particular preparation of procaine penicillin requires consideration of the limits imposed by the clearance data presented.

Penicillin clearances in premature infants suggest that if penicillin is given to small infants in dosages proportionate to their surface area, the duration of drug concentrations in the blood should be six times as long as in children and adults and three times as long if the dosage is proportionate to body weight.

Acknowledgment

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SPANISH ABSTRACT

Eliminaciones Renales de Penicilina G de Sodio, Penicilina G de Procaina, e Inulina en Infantes y Niños

Los informes de inesperadas concentraciones de alto suero de penicilina G de procaina sugirieron que en adición a la absorción lenta, la eliminación renal de penicilina de procaina podía ser más baja que la de la sal de sodio. Las medidas de las eliminaciones de inulina y las eliminaciones de penicilina G de sodio o penicilina G de procaina en diez niños y cuatro infantes prematuros no mostró significante diferencia entre las eliminaciones de las dos sales de penicilina; por consiguiente, una eliminación reducida de penicilina de procaina no explica el suceso aparente de inesperadas concentraciones de alto suero de penicilina en sujetos normales. La valuación crítica de los informes sobre el mantenimiento de las cantidades de drogas con una preparación de penicilina de procaina requiere consideración de los límites impuestos. Las eliminaciones de penicilina en infantes prematuros sugiere que si se les da penicilina a infantes pequeños en dosis en proporción a su área de superficie, la duración de las concentraciones de droga en la sangre debe de ser seis veces tan larga como en niños y adultos y tres veces tan larga si la dosis es en proporción al peso del cuerpo.

525 E. 68th St.

A SIMPLIFIED INFUSION SET FOR INFANTS

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SIMPLIFICATION of pediatric infusion and transfusion apparatus has been the subject of extensive clinical experimentation. Since 1900, there have been more than seventy published reports[1] on various transfusion assemblies. Most of these were designed primarily for adult intravenous therapy and consequently were too cumbersome and inefficient to use for pediatric infusion therapy. Also, many of them required multiple operators.

Transfusion technic has been given added impetus in the Tulane Pediatric Division of Charity Hospital, where almost all acutely ill infants and children receive parenteral fluids. A systematic program was begun for the purpose of devising a simplified practical infusion assembly that would appeal to house staff and private practitioners alike. All pediatric services, premature, infant and juvenile wards, with their large number of dangerously ill patients who required rapid fluid replacement, were included in the program.

The final assembly which proved satisfactory in more than a thousand procedures performed by the resident staff and interested private practitioners is composed of the following parts: 1. one 23 or 24 gauge short bevel needle, 4 cm. in length, 2. one continuous-flow automatic valve (Fig. 1),* 3. one Hoffman clamp, 4. one 5 cc. Luer-Lok syringe, 5. 150 cm. of thin transparent rubber tubing, 6. one special ("Aloe") sleeve-type bottle-stopper.* 7. one straight-tube pyrex connection, 8. the proximal 20 cm. of a no. 18 French rubber catheter. (See Fig. 2 for assembly.)

This set is operated satisfactorily in the following manner: the pumping portion is checked prior to use by loading the entire circuit (Fig. 3), and by pumping after inserting the catheter portion of the assembly in a reservoir bottle of normal saline; this fills the tubing and so rids the system of air. Caution should be taken during this maneuver to avoid contaminating the catheter or sleeve stopper. The sterile catheter portion of the loaded circuit is then transferred to another reservoir bottle containing the fluid to be administered. The site of venipuncture is chosen; in almost all cases we have selected veins of the scalp (superficial temporal), hand (dorsal metacarpal), or arm (basilic and median cubital). With the loaded syringe of the assembly in the right hand, the operator assumes a comfortable and convenient position. The sharp but short bevel needle is introduced into a superficial vein; entrance is successful if no fluid accumulates about the needle point after slight pressure is exerted on the piston of the syringe. To prevent dislodgment of the needle, pressure from the distal phalanx of the left middle finger should be exerted over the skin covering the proximal portion of the needle, with the thumb and index finger firmly grasping the Hoffman clamp attached to the hub of the needle (Fig. 3). The apparatus can be comfortably held in this position for long

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periods of time. The "push-pull" action of the syringe piston furnishes a continuous flow into the needle; constant pressure on the piston is necessary to keep the small T-valve (Fig. 1) in the closed position while fluid is being administered. Back flow of fluid indicates either insufficient piston pressure, or that a worn rubber T-valve should be replaced. "Sticking" of syringes can be avoided by application of a small drop of mineral oil to the piston of the syringe before sterilization; the use of small syringes (2 cc. Luer-Lok or 1 cc. tuberculin type) also reduces the frequency of this occasional nuisance. Im-

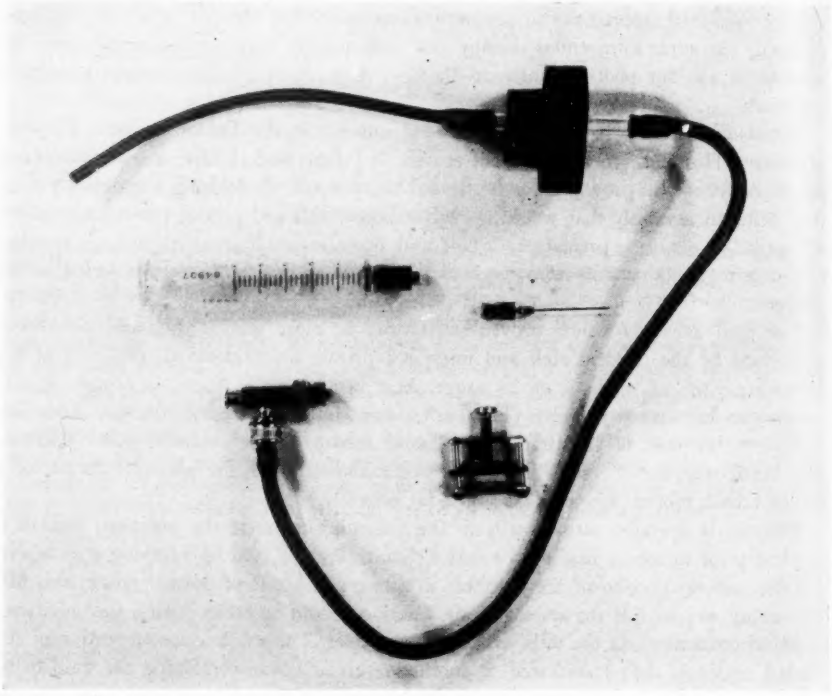

FIG. 1. Parts for infusion set.

mediately following completion of each transfusion, the circuit should be cleansed by pumping cold water through it five or six times; then, as soon as convenient, the entire apparatus, particularly the automatic valve, should be taken apart, washed with soap and water, and thoroughly rinsed with distilled water.

When the apparatus is returned to the supply room, the following cleansing routine is used: 1. thorough flushing and rinsing of the entire assembly first with a 25% hydrogen peroxide solution and then with distilled water. One small drop of sterile mineral oil is applied to the syringe plunger, the set is assembled, placed in a folded towel, tied securely and autoclaved for 15 minutes at 137.7° C. under 18 pounds of pressure. The "T" pieces in the automatic valve should be replaced after they have been used about 15 times. New untreated tubing is made safe by, 1. boiling for 30 minutes in a solution of

2% sodium hydroxide, 2. rinsing in tap water, 3. soaking for 30 minutes in a solution of 1% hydrochloric acid, 4. rinsing with tap water, and finally with distilled water. Since translucent intravenous tubing latex type,* available commercially, has already been so treated, only the hydrogen peroxide cleaning routine is necessary.

DeBakey[1] makes this well-advised statement: "It is the lack of appreciation of ostensibly minor details and technical difficulties which may arise during the operation of an intravenous apparatus that is responsible for the majority of failures in the procedure

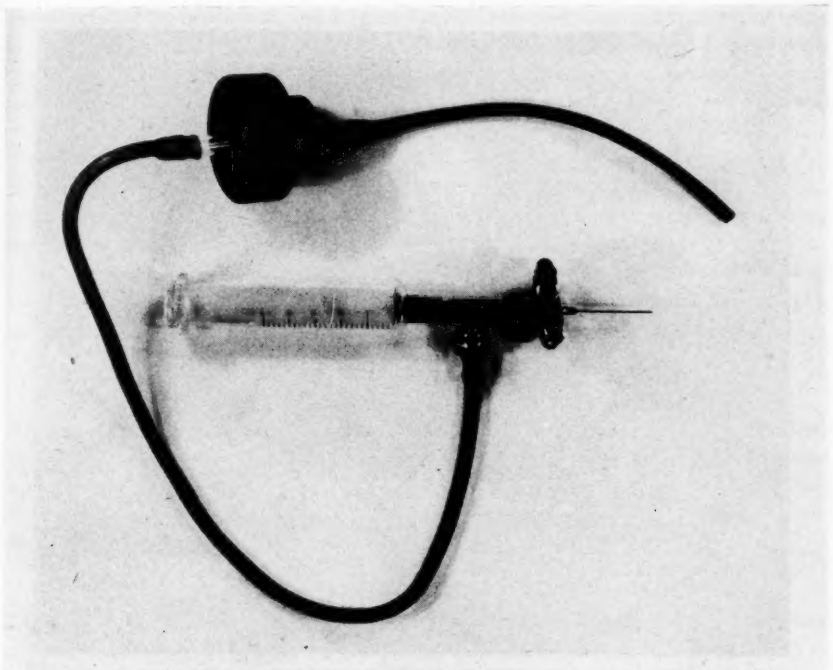

FIG. 2. Apparatus assembled.

of blood transfusion." We wish to direct attention to these details and to emphasize means of preventing failures.

Following are some errors that the beginner is apt to make with this apparatus:

1. Failure to load circuit with normal saline or 5% glucose solution and to check valve action before insertion into vein.
2. Failure to check Luer-Lok connections for leakage before use.
3. Too wide variations in force applied to syringe plunger.
4. Failure to agitate citrated blood occasionally in reservoir bottle during transfusion.
5. Improper position of fingers, failure to hold needle firmly in vein.

* B. F. Goodrich Co., Akron, Ohio.

6. Failure to rinse apparatus immediately after use.
7. Failure to replace rubber T-valves after 15 transfusions. All poorly fitted, worn, or overheated rubber T-valves should be discarded; their cost is negligible.

With this assembly, the operator has all phases of the entire procedure under his direct control. Furthermore, one hand is free most of the time to deal with any unexpected difficulties that may arise. In most cases, no trained assistance is necessary.

This closed circuit apparatus may be conveniently used for 1. bone marrow infusions,[2] 2. transfusions of whole blood, 3. administration of four times concentrated plasma,

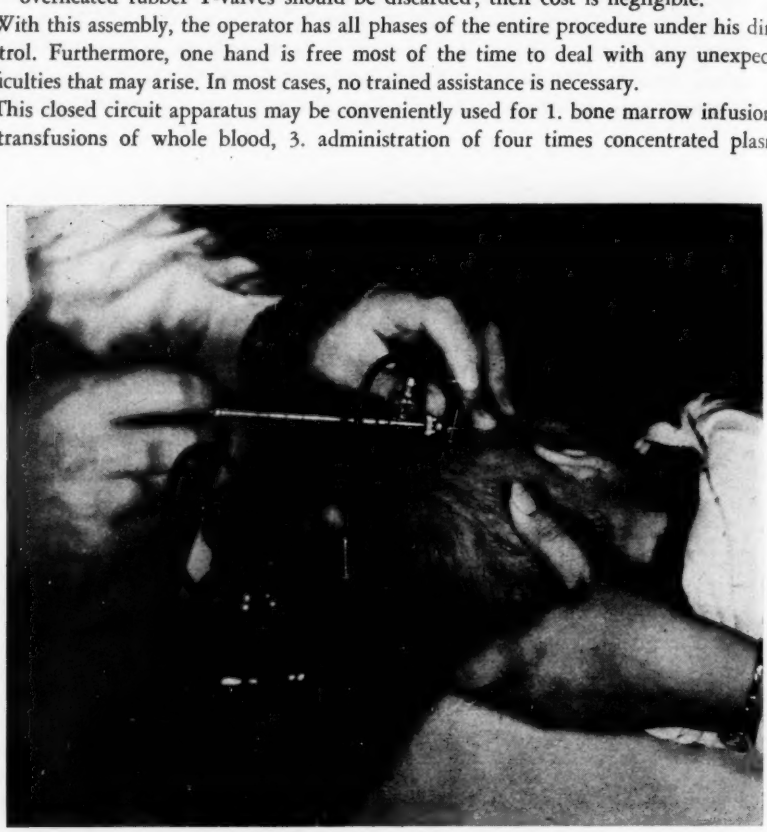

FIG. 3. Operation of assembly.

4. rapid-force transfusion for states of shock,[3] 5. transfusion of washed maternal cells for erythroblastotic infants, 6. "exsanguination" or "replacement" transfusions for erythroblastotic infants (two sets working simultaneously, one in vein for blood replacement, other attached in suction position to plastic polyethylene tubing inserted into umbilical vein for blood removal), and 7. in adults, rapid transfusion in treating massive obstetric hemorrhage. Cole[4] states, "When a patient is suffering shock from massive blood loss, the ordinary drip method is wholly unsuitable. Forty per cent of total blood lost should be replaced in one hour." With this apparatus pumping blood into an arm vein, rapid replacement is easily facilitated, and exceedingly large volumes lost can be replaced quickly. Successful use of this assembly in over 300 bone marrow infusions in infants has been reported.[2]

There is considerable variation of opinion regarding the rate of administration of

blood. Some believe that blood should be given slowly, whereas others think that this has been overemphasized. DeBakey and Kilduffe[1] point out that the possible danger of too rapid administration has been overemphasized, has little rational basis, and has not been demonstrated adequately by experimental study. Speed shock as described by Hirschfield[5] may often be better explained by incompatibility of blood.[6] If large amounts of fluids are needed for infants, one should proceed slowly however; we have not exceeded a rate of 10 cc./min. up to a total amount approximately 22 cc./kg. of body weight; this is roughly equivalent to about one fourth of the infant's total blood volume.[7] If a changeover to a continuous drip is desired after initial pumping, the assembly can be disconnected at the needle hub, and a lightweight B-D adapter, Luer-Lok type,* inserted so as to connect the needle hub to a regular drip infusion set. Needles should be carefully taped in place; the Hoffman clamp attached to the hub serves as a convenient taping anchor. Application of a 1.5 cm. continuous-traction tape† over the adhesive tape will provide a firm needle insertion that may remain in place longer.

Those using Baxter‡ or Cutter§ transfusion sets as standard equipment will find it necessary to remove the rubber stopper and diaphragm completely, or to transfer contents to another sterile container in order that the handy sleeve-stopper of this assembly can be used.

Since the pediatric service has been using this assembly very few "cut-down" procedures have been necessary. The assembly is inexpensive,‖ compact (25 cm. by 12.5 cm), and can be easily carried in a physician's bag.

Summary

A simple, convenient, and compact apparatus for infusion and transfusion is described. Its advantages and some common errors encountered during its use in over a thousand infusions and transfusions to infants and children are discussed. Detailed instruction for assembly and operation are given, and its convenience in home or hospital is emphasized.

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* Becton, Dickinson and Co., Rutherford, N.J.
† Davol Rubber Co., Providence, R.I.
‡ Baxter Laboratories, Glenview, Ill.
§ Cutter Laboratories, Berkeley, Calif.
‖ Total cost (estimated by A. S. Aloe Company) is $7.00.

SPANISH ABSTRACT

Aparato de infusión, simplificado, para uso en infantes

Este aparato puede hacerse con partes fáciles de obtener, y ha probado ser muy práctico y conveniente para uso rutinario, especialmente en infantes. Se incluyen instrucciones completas para juntar y usar el aparato.

412 Third St.

BCG TUBERCULIN STUDIES

An Experimental and Clinical Investigation

By J. HENNING MAGNUSSON, M.D., AND A. LITHANDER, M.D.
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IN SWEDEN a great many infants are being vaccinated against tuberculosis. Calmette vaccination is performed on one of the first days of life, when the child is still in an obstetric ward, and before it has been exposed to tuberculous infection.

There are, however, certain difficulties in connection with vaccination at such an early age. In his latest general report on Calmette vaccination in Sweden, Wallgren writes as follows: "Newborns and infants are remarkably insensitive to BCG vaccine. The ordinary BCG dose will frequently fail to produce tuberculin sensitiveness, the reaction developing at the site of injection being very slight or none. Even in those cases where a reaction ensues, the children do not usually become tuberculin sensitive until a considerable period has elapsed." This reaction in newborns and infants is of great practical significance and was the direct incentive for the present investigation.

It is biologically possible that tuberculin prepared from the BCG strain might prove superior to ordinary standard tuberculin in producing positive reactions in Calmette-vaccinated infants, especially in newborns, at an earlier stage. After careful discussion of the problem it was decided to investigate this aspect and to supplement clinical experiments with those on animals. Apart from minor interruptions, the work has been carried on since June 1945.

PREPARATION AND TESTING OF BCG TUBERCULIN

The tuberculin was prepared from BCG cultures grown as routine on Sauton's medium for the production of BCG vaccine. The BCG organisms were allowed to grow for 11 to 12 days and were then separated from the medium. The substrate was tested for freedom from other bacteria and passed through paper and Seitz filters. It was then heated at 60° C. for 24 hours and subjected to the usual sterility tests. In order to exclude the presence of viable virulent tubercle bacilli, two guinea pigs were injected with 1 ml. each of the fluid. The latter, which was termed BCG tuberculin, was transferred into ampoules and stored in a refrigerator at +4° C.

The potency of the BCG tuberculin was determined by comparison both with standard old tuberculin and with a particular batch of commercial tuberculin. The testing was carried out by means of intradermal injections in guinea pigs infected with virulent tubercle bacilli six to seven weeks previously. Initially two strains were used, one bovine and one human. Since both strains were shown to give uniform results, only bovine tubercle bacilli, i.e., the strain K_3, were used subsequently. At this stage as well as later, the commercial tuberculin used in a given experiment was always prepared from that type of tubercle bacilli with which the animals in that experiment were infected. The titration was performed in two steps for each batch of BCG tuberculin. The first was a rough estimate. On the basis of the result obtained, exact titration was carried out with the same animal a week later. It was thus possible to take into account the individual variations shown by the animals.

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Paper read on March 8, 1948, to the Section for Hygiene and Bacteriology of the Swedish Medical Association and to the Section for Pediatrics and School Hygiene on March 12, 1948.

(Received for publication July 30, 1948.)

In the first test the BCG tuberculin was diluted 1:4, 1:6, 1:9 or 1:5, 1:7.5, 1:11.25 and the standard tuberculin 1:100, 1:150, 1:225. 0.1 ml. of each dilution was injected into the shaved dorsal skin. The exact titration was based on those dilutions of BCG tuberculin and standard tuberculin respectively that most nearly gave a reaction measuring 10 mm. in diameter. The following example may be quoted. If the dilutions 1:7.5 and 1:150 respectively had produced reactions of about 10 mm. in diameter, three injections were made of the standard tuberculin diluted 1:150 and of the BCG tuberculin dilutions 0.8:7.5, 1.0:7.5 and 1.25:7.5.

Since certain writers state that various areas of the skin of guinea pigs differ as to reactivity, the sites of the injections were as shown in Fig. 1. In the comparative tests with standard old tuberculin and commercial tuberculin a total of 20 guinea pigs was used for each batch of BCG tuberculin.

Animal Experiments

Details of Procedure

Guinea pigs were infected with viable BCG organisms. Intradermal reactions provoked by commercial tuberculin were compared with those from the BCG tuberculin. The principal object was to

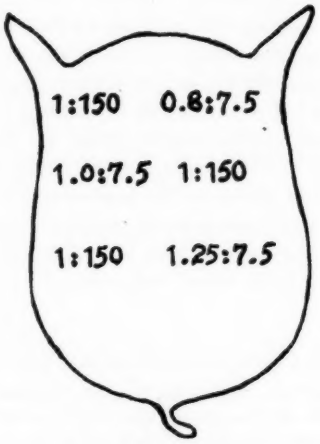

Fig. 1. Sites of injection.

ascertain whether the two types of tuberculin differed in their power of evoking positive reactions at various times after infection with BCG vaccine. A reddened zone of a wheal at least 10 mm. in diameter was regarded as evidence of a positive reaction.

The inoculations were made with ordinary BCG vaccine. Since preliminary investigations showed a large dose to be appropriate, 15 mg. was selected. In four series comprising altogether 118 guinea pigs, this amount of BCG vaccine was injected subcutaneously into the right thigh. Tuberculin tests were performed on these animals 6, 7, 8, 9, 11 and 13 weeks after infection with BCG organisms. The tuberculin was injected into the dorsal skin. One or 0.5 mg. of the commercial tuberculin was injected, and of the BCG tuberculin those amounts that previous titration had proved equivalent to 1.0 and 0.5 mg., respectively, of the commercial tuberculin.

In order to avoid overlooking possible nonspecific reactions, controls were made as follows: An amount of Sauton's medium equivalent to the larger dose of BCG tuberculin and of glycerol broth equivalent to 1.0 mg. of commercial tuberculin was injected. The controls were examined after 48 hours. In those instances where the control injections caused reactions, such areas were subtracted from those of the corresponding reactions to tuberculin. The tuberculin tests were then considered positive if the remaining area was equivalent to a circle with a minimal diameter of 10 mm.

The BCG tuberculin reactions were similar in appearance to those from ordinary tuberculin. Like the reactions provoked by commercial tuberculin they could be observed as early as after 24 hours,

the flare at that time usually being larger than that remaining after 48 hours. As a rule, injections of the two media failed to give reactions in the tests made six and seven weeks respectively after infection, but could arise later. Reactions were rare with Sauton's medium, but considerably more frequent with glycerol broth, when they were also somewhat larger.

As controls for the infection experiments with BCG organisms, four experimental series, comprising altogether 121 guinea pigs, were used. The animals were infected with virulent tubercle bacilli. In one of the control series a human strain was used; in the remaining three, the bovine strain, K_3. 0.15 mg. of the virulent bacilli was injected into each of the animals, with 0.05 mg. of these causing definite tuberculous lesions.

Results of Experiments

The results are seen in Tables I and II. Table I shows that, in BCG-infected guinea pigs, "1.0" mg. and "0.5" mg. of BCG tuberculin evoked positive reactions more fre-

TABLE I

Intradermal Tuberculin Tests in Guinea Pigs Infected with 15 mg. of BCG Vaccine. "1.0" mg. and "0.5" mg. = Doses of BCG Tuberculin Equivalent to 1.0 mg., and 0.5 mg., Respectively, of Commercial Tuberculin. P = Percentage of Positive Tuberculin Tests. E/P/ = Standard Error in the Percentage

Date of infection	Series no.	Number of weeks after infection	Total number of surviving animals	BCG tuberculin				Commercial tuberculin			
				Positive to "1.0" mg.		Positive to "0.5" mg.		Positive to 1.0 mg.		Positive to 0.5 mg.	
				Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)
15/4 1946	I	6	22	15	68.2± 9.9	11	50.0±10.7	1	4.5± 4.4	0	—
		7	22	15	68.2± 9.9	11	50.0±10.7	4	18.2± 8.2	0	—
		8	20	17	85.0± 8.0	11	55.0±11.1	7	35.0±10.7	1	5.0± 4.9
		9	18	15	83.3± 8.8	9	50.0±11.8	9	50.0±11.8	1	5.6± 5.4
		11	17	14	82.4± 9.2	8	47.1±12.1	11	64.7±11.6	1	5.9± 5.7
		13	15	12	80.0±10.3	7	46.7±12.9	10	66.7±12.2	1	6.7± 6.5
8/5 1946	II	6	33	25	75.8± 7.5	11	33.3± 8.2	0	—	0	—
		7	32	27	84.4± 6.4	13	40.6± 8.7	7	21.9± 7.3	0	—
		8	28	26	92.9± 4.9	12	42.9± 9.4	10	35.7± 9.1	0	—
		9	27	26	96.3± 3.6	12	44.4± 9.6	16	59.3± 9.5	2	7.4± 5.0
		11	27	26	96.3± 3.6	12	44.4± 9.6	21	77.8± 8.0	3	11.1± 6.0
		13	27	26	96.3± 3.6	12	44.4± 9.6	22	81.5± 7.5	3	11.1± 6.0
17/7 1946	III	6	31	24	77.4± 7.5	18	58.1± 8.9	5	16.1± 6.6	0	—
		7	30	25	83.3± 6.8	22	73.3± 8.1	5	16.7± 6.8	0	—
		8	30	25	83.3± 6.8	24	80.0± 7.3	7	23.3± 7.7	0	—
		9	30	26	86.7± 6.2	25	83.3± 6.8	13	43.3± 9.0	2	6.7± 4.6
		11	29	26	89.7± 5.6	25	86.2± 6.4	19	65.5± 8.8	3	10.3± 5.6
		13	29	26	89.7± 5.6	25	86.2± 6.4	19	65.5± 8.8	3	10.3± 5.6
5/12 1946	IV	6	35	26	74.3± 7.4	14	40.0± 8.3	5	14.3± 5.9	0	—
		7	32	26	81.3± 6.9	23	71.9± 7.9	10	31.3± 8.2	1	3.1± 3.1
		8	31	26	83.9± 6.6	24	77.4± 7.5	18	58.1± 8.9	10	32.3± 8.4
		9	28	24	85.7± 6.6	22	78.6± 7.8	18	64.3± 9.1	10	35.7± 9.1
		11	25	23	92.0± 5.4	20	80.0± 8.0	17	68.0± 9.3	12	48.0±10.0
		13	23	21	91.3± 5.9	18	78.3± 8.6	17	73.9± 9.2	15	65.2± 9.9
Summary of series I, II, III and IV		6	121	90	74.4± 4.0	54	44.6± 4.5	11	9.1± 2.6	0	—
		7	116	93	80.2± 3.7	69	59.5± 4.6	26	22.4± 3.9	1	0.9± 0.9
		8	109	94	86.2± 3.3	71	65.1± 4.6	42	38.5± 4.7	11	10.0± 2.9
		9	103	91	88.3± 3.2	68	66.0± 4.7	56	54.4± 4.9	15	14.6± 3.5
		11	98	89	90.8± 2.9	65	66.3± 4.8	68	69.3± 4.7	19	19.4± 4.0
		13	94	85	90.4± 3.0	62	66.0± 4.9	68	72.3± 4.6	22	23.4± 4.4

quently in tests following close upon infection than did 1.0 mg. and 0.5 mg. of commercial tuberculin. The figures given in the summary of the table show that the differences between the BCG tuberculin doses of "1.0" mg. and "0.5" mg. and the commercial tuberculin doses of 1.0 mg. and 0.5 mg., respectively, are significant at all the times investigated after infection. On examining the different experimental series separately we find the following: In the tests carried out shortly after infection the BCG tuberculin

TABLE II

INTRADERMAL TUBERCULIN TESTS IN GUINEA PIGS INFECTED WITH 0.15 MG. OF VIRULENT TUBERCLE BACILLI. IN SERIES I ANIMALS WERE INFECTED WITH HUMAN STRAIN, IN OTHERS WITH BOVINE STRAIN, K_3

Date of infection	Series no.	Number of weeks after infection	Total number of surviving animals	BCG tuberculin				Commercial tuberculin			
				Positive to "1.0" mg.		Positive to "0.5" mg.		Positive to 1 mg.		Positive to 0.5 mg.	
				Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)
15/4 1946	I	6	23	14	60.9 ± 10.2	11	47.8 ± 10.4	13	56.5 ± 10.3	7	30.4 ± 9.6
		7	23	16	69.6 ± 9.6	12	52.2 ± 10.4	15	65.2 ± 9.9	8	34.8 ± 9.9
		8	23	18	78.3 ± 8.6	14	60.9 ± 10.2	18	78.3 ± 8.6	9	39.1 ± 10.2
		9	23	18	78.3 ± 8.6	14	60.9 ± 10.2	18	78.3 ± 8.6	9	39.1 ± 10.2
		11	23	18	78.3 ± 8.6	14	60.9 ± 10.2	20	87.0 ± 7.0	10	43.5 ± 10.3
		13	23	18	78.3 ± 8.6	14	60.9 ± 10.2	20	87.0 ± 7.0	10	43.5 ± 10.3
8/5 1946	II	6	32	30	93.8 ± 4.3	21	65.6 ± 8.4	23	71.9 ± 7.9	11	34.4 ± 8.4
		7	32	30	93.8 ± 4.3	21	65.6 ± 8.4	30	93.8 ± 4.3	18	56.3 ± 8.8
		8	32	31	96.9 ± 3.1	22	68.8 ± 8.2	32	100.0	19	59.4 ± 8.7
		9	32	32	100.0	22	68.8 ± 8.2	32	100.0	19	59.4 ± 8.7
		11	32	32	100.0	22	68.8 ± 8.2	32	100.0	19	59.4 ± 8.7
		13	32	32	100.0	22	68.8 ± 8.2	32	100.0	19	59.4 ± 8.7
17/7 1946	III	6	30	29	96.7 ± 3.3	28	93.3 ± 4.6	29	96.7 ± 3.3	27	90.0 ± 5.5
		7	30	29	96.7 ± 3.3	28	93.3 ± 4.6	29	96.7 ± 3.3	27	90.0 ± 5.5
		8	32	31	96.7 ± 3.3	28	93.3 ± 4.6	29	96.7 ± 3.3	27	90.0 ± 5.5
		9	30	29	96.7 ± 3.3	28	93.3 ± 4.6	29	96.7 ± 3.3	27	90.0 ± 5.5
		11	30	29	96.7 ± 3.3	28	93.3 ± 4.6	29	96.7 ± 3.3	27	90.0 ± 5.5
		13	29	29	100.0	28	96.6 ± 3.4	29	100.0	27	93.1 ± 4.7
5/12 1946	IV	6	33	23	69.7 ± 8.0	18	54.5 ± 8.7	25	75.8 ± 7.5	15	45.5 ± 8.7
		7	30	27	90.0 ± 5.5	21	70.0 ± 8.4	25	83.3 ± 6.8	21	70.0 ± 8.4
		8	29	27	93.1 ± 4.7	27	93.1 ± 4.7	28	96.6 ± 3.4	27	93.1 ± 4.7
		9	28	27	96.4 ± 3.5	27	96.4 ± 3.5	28	100.0	27	96.4 ± 3.5
		11	28	27	96.4 ± 3.5	27	96.4 ± 3.5	28	100.0	27	96.4 ± 3.5
		13	28	27	96.4 ± 3.5	27	96.4 ± 3.5	28	100.0	27	96.4 ± 3.5
Summary of Series I, II III and IV.		6	118	96	81.4 ± 3.6	78	66.1 ± 4.4	90	76.3 ± 3.9	60	50.8 ± 4.6
		7	115	102	88.7 ± 3.0	82	71.3 ± 4.2	99	86.1 ± 3.2	74	64.3 ± 4.5
		8	114	105	92.1 ± 2.5	91	79.8 ± 3.8	107	93.9 ± 2.2	82	71.9 ± 4.2
		9	113	106	93.8 ± 2.3	91	80.5 ± 3.7	107	94.7 ± 2.1	82	72.6 ± 4.2

proved superior to the corresponding doses of commercial tuberculin. In one of the series this superiority is apparent only in the tests made six and seven weeks after infection. In the remaining series this is also the case in the test performed eight weeks after inoculation of BCG organisms. It is also evident that in early tests "0.5" mg. of BCG tuberculin caused positive reactions to a greater extent than 1.0 mg. of commercial tuberculin.

It is seen from Table II that positive reactions in guinea pigs infected with virulent

tubercle bacilli are as frequent with commercial tuberculin as with BCG tuberculin. A significant difference occurs only in Series 2, a test with 0.5 mg. six weeks after infection.

The development of the tuberculin reactions is illustrated by Figs. 2 and 3.

In the experimental series recorded in the foregoing the tuberculin tests were made after 6, 7, 8, 9, 11 and 13 weeks, counting from the day on which the animals were inoculated. In order to ascertain whether these repeated tuberculin injections could exert a sensitizing or desensitizing action upon the animals, the following experiments were

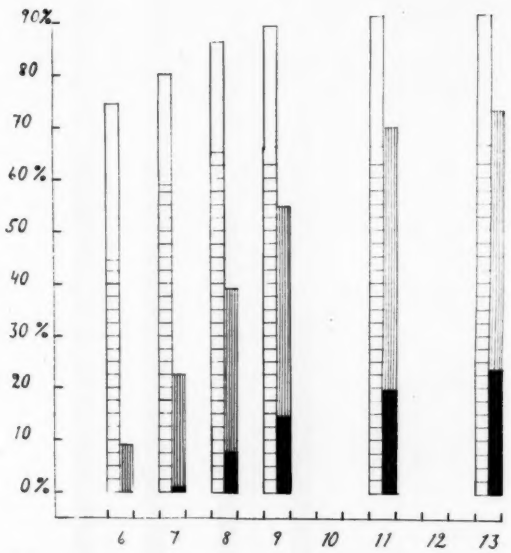

FIG 2. Guinea pigs infected with BCG vaccine (numerical data from the summary of Table I). In Figs. 2 and 3 the figures in the ordinate give the percentage of animals with positive tuberculin tests, and those in the abscissa, the numbers of weeks after infection with BCG vaccine. The following symbols are used:

□ = "1.0" mg. of BCG tuberculin

▤ = "0.5" mg. of BCG tuberculin

▥ = 1.0 mg. of commercial tuberculin

■ = 0.5 mg. of commercial tuberculin

made. Two series of guinea pigs were infected with BCG vaccine, tuberculin tests being made twice only, i.e., 6 and 11 weeks after inoculation. For the results, see Table III.

As is seen from Table III, in these two experimental series the results were, in principle, in agreement with those shown in Table I. Thus the tuberculin injections repeated at shorter intervals in the preceding experiments would not seem to have caused either sensitization or desensitization.

The results of the tests with BCG tuberculin in BCG-infected guinea pigs six weeks after infection (Tables I and III) suggest that even earlier positive reactions might be obtained. A series of guinea pigs infected with BCG vaccine was therefore tested with

tuberculin three, four and five weeks after infection. The results of these tests are shown in Table IV.

The figures in Table IV show that the reaction to BCG tuberculin was positive as early as three weeks after infection in a considerable number of cases. The incidence of positive reactions increased gradually, and four weeks after infection more than half the animals reacted to BCG tuberculin. No positive reaction to commercial tuberculin could

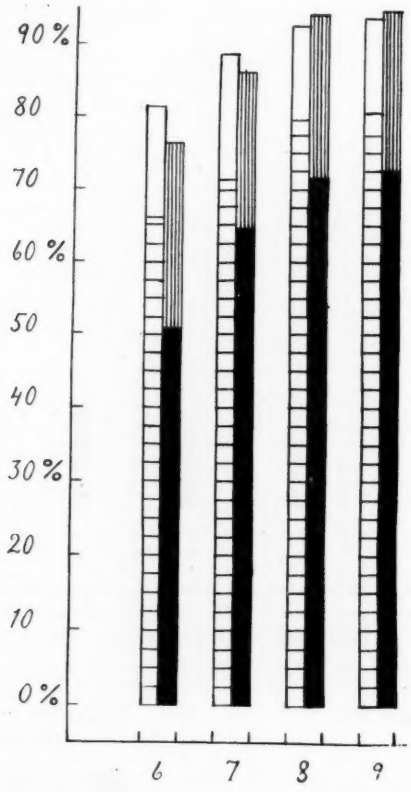

FIG. 3. Guinea pigs infected with virulent tubercle bacilli (numerical data from the summary of Table II). Symbols as in Fig. 2.

be observed three and four weeks after inoculation. Not until five weeks after infection did some few animals react to this tuberculin.

The tuberculins used in all the above experiments were prepared by means of two different substrates, i.e., the commercial tuberculin with glycerol broth, and the BCG tuberculin with Sauton's medium. In order to ascertain whether the difference in the media used had influenced the results described in the foregoing, experiments were performed in which a tuberculin was prepared from a virulent bovine strain (K_3) grown on Sauton's medium and compared with equivalent amounts of BCG tuberculin. The

TABLE III

INTRADERMAL TUBERCULIN TESTS IN GUINEA PIGS INFECTED WITH 15 MG. OF BCG VACCINE

Date of infection	Number of weeks after infection	Total number of surviving animals	BCG tuberculin				Commercial tuberculin			
			Positive to "1.0" mg.		Positive to "0.5" mg.		Positive to 1.0 mg.		Positive to 0.5 mg.	
			Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)
21/11 1946	6	36	30	83.3±6.2	24	66.7±7.9	11	30.6±7.7	0	—
	11	29	26	89.7±5.6	26	89.8±5.6	23	79.3±7.5	18	62.1±9.0
26/11 1946	6	37	26	70.3±7.5	20	54.1±8.2	6	16.2±6.1	0	—
	11	33	26	78.8±7.1	21	63.6±8.4	12	36.4±8.4	5	15.2±6.2

TABLE IV

INTRADERMAL TUBERCULIN TESTS IN GUINEA PIGS INFECTED WITH 15 MG. OF BCG VACCINE

Date of infection	Number of weeks after infection	Total number of surviving animals	BCG tuberculin				Commercial tuberculin			
			Positive to "1.0" mg.		Positive to "0.5" mg.		Positive to 1.0 mg.		Positive to 0.5 mg.	
			Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)
11/11 1946	3	38	15	39.5±7.9	11	28.9±7.4	0	—	0	—
	4	38	22	57.9±8.0	16	42.1±8.0	0	—	0	—
	5	37	24	64.9±7.8	19	51.4±8.2	5	13.5±5.6	0	—

TABLE V

INTRADERMAL TUBERCULIN TESTS IN GUINEA PIGS INFECTED WITH 15 MG. OF BCG VACCINE. TUBERCULIN K_3S_1 = TUBERCULIN PREPARED FROM THE STRAIN K_3 GROWN ON SAUTON'S MEDIUM

Date of infection	Number of weeks after infection	Total number of surviving animals	BCG tuberculin				Tuberculin K_3S_1			
			Positive to "1.0" mg.		Positive to "0.5" mg.		Positive to 1.0 mg.		Positive to 0.5 mg.	
			Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)
13/5 1947	6	38	29	76.3±6.9	20	52.6±8.1	15	39.5±7.9	4	10.5±5.0
	7	37	31	83.8±6.1	20	54.1±8.2	15	40.5±8.1	5	13.5±5.6
	8	37	32	86.5±5.6	28	75.7±7.1	23	62.2±8.0	14	37.8±8.0
	9	35	30	85.7±5.9	27	77.1±7.1	23	65.7±8.0	18	51.4±8.4
	11	33	30	90.9±5.0	27	81.8±6.7	25	75.8±7.5	21	63.6±8.4

procedure was the same as in the previous experiments. The results are shown in Tables V and VI.

As is shown by Table V, the incidence of positive reactions to BCG tuberculin was in agreement with the results obtained in preceding experimental series, being higher than the number of positive reactions caused by tuberculin.

Tests in Children

Details of Procedure

The period during which the BCG vaccine was used did not exceed one week, counting from the date of preparation. The vaccine was stored in a refrigerator. Before removing the vaccine from the ampoules, the latter were shaken vigorously. In order to exclude infection owing to bacterial contamination of the vaccine, the ampoules were discarded after one day. The BCG vaccine was administered intradermally in the left external femoral region after washing the skin with ether, the dose being 0.1 ml. (0.05 mg.). As a rule newborns were vaccinated on one of the first days of life and without previous tuberculin tests. Older infants were vaccinated only after proving tuberculin-negative to 1.0 mg. (Mantoux test). In those instances where exposure to tuberculous infection was either established or suspected, the children were excluded from the material.

TABLE VI

Intradermal Tuberculin Tests in Guinea Pigs Infected with 0.15 mg. of the Bovine Strain K_2

Date of infection	Number of weeks after infection	Total number of surviving animals	BCG tuberculin				Tuberculin K_2S_1			
			Positive to "1.0" mg.		Positive to "0.5" mg.		Positive to 1.0 mg.		Positive to 0.5 mg.	
			Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)	Numbers	Percentage rates P ± E(P)
13/5 1947	6	39	34	87.2±5.3	25	64.1±7.7	37	94.9±3.5	26	66.7±7.5
	7	39	38	97.4±2.5	33	84.6±5.8	39	100.0	35	89.7±4.9
	8	39	38	97.4±2.5	35	89.7±4.9	39	100.0	35	89.7±4.9
	9	39	38	97.4±2.5	35	89.7±4.9	39	100.0	35	89.7±4.9
	11	39	38	97.4±2.5	35	89.7±4.9	39	100.0	36	92.3±4.3

TABLE VII

Ages	0–3 mos.	3–6 mos.	6–12 mos.	1–2 yrs.	2–3 yrs.	3–6 yrs.	6–12 yrs.
Number of cases examined	9	16	21	17	14	11	12

The BCG-vaccinated children were protected from exposure to virulent infection until their tuberculin sensitivity had developed. In the tuberculin tests carried out on vaccinated children, 1.0 mg. of commercial tuberculin and the equivalent amount ("1.0" mg.) of BCG tuberculin were used. The tuberculins were stored in a refrigerator, the period of use not exceeding one week for a given ampoule. In these tests the reactions were considered positive where a wheal and flare at least 10 mm. in diameter was found on examination after three days (72 hours).

To prevent possible nonspecific reactions from escaping observation, the tuberculin tests after BCG vaccination were supplemented in 100 cases by control tests with glycerol broth in amounts corresponding to 1.0 mg. of commercial tuberculin, and with Sauton's medium in amounts equivalent to "1.0" mg. of BCG tuberculin. There were no pseudoreactions when the tuberculin tests were read after 72 hours. Any such possible reactions must therefore have subsided prior to that moment. During the later part of the investigation no such controls were made.

For the same reason the following experiments were carried out. In 100 definitely tuberculin-negative, not BCG-vaccinated children, the Mantoux reactions were compared after 1.0 mg. of commercial tuberculin and "1.0" mg. of BCG tuberculin. On examination after 72 hours the tests were negative in all cases. In four cases the commercial tuberculin caused a flare of about 3 by 3 mm., and in two the BCG tuberculin gave a flare measuring 2 by 2 mm. The age distribution within this series is seen from Table VII.

Results of Tests

The results are shown in Tables VIII, IX and X, as well as in Fig. 4. As is shown by the figures in Table VIII, in the first tuberculin tests after BCG vaccination the

TABLE VIII

INTRADERMAL TUBERCULIN TESTS IN 491 INFANTS BCG-VACCINATED DURING FIRST WEEK OF LIFE (USUALLY ON ONE OF FIRST 3 DAYS OF LIFE). COMPARISON BETWEEN 1.0 MG. OF COMMERCIAL TUBERCULIN AND EQUIVALENT AMOUNT ("1.0" MG.) OF BCG TUBERCULIN. IN EACH OF THESE CASES TEST WAS FIRST TO BE MADE AFTER VACCINATION

Number of weeks after vaccination	Total number of children tested with tuberculin	Positive to 1.0 mg. of commercial tuberculin		Positive to "1.0" mg. of BCG tuberculin	
		Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)
4	1				
5	38	12	31.6±7.6	37	97.3±2.8
6	166	73	44.0±3.9	141	84.9±2.8
7	81	51	63.0±5.4	75	92.6±2.8
8	80	50	62.5±5.4	75	93.8±2.7
9–11	72	47	65.3±5.6	69	95.7±2.3
>11	53	50	94.3	53	100.0

TABLE IX

INTRADERMAL BCG TUBERCULIN TESTS IN 810 INFANTS BCG-VACCINATED DURING FIRST WEEK OF LIFE (USUALLY ON ONE OF FIRST 3 DAYS OF LIFE). IN EVERY ONE OF THESE CASES TEST WAS FIRST ONE TO BE MADE AFTER VACCINATION

Number of weeks after vaccination	Total number of children tested with tuberculin	Positive to "1.0" mg. BCG tuberculin	
		Number	Percentage rates P±E(P)
5	19	16	84.2±8.4
6	297	259	87.2±1.9
7	184	168	91.3±2.1
8	80	74	92.5±3.0
9–11	118	110	93.2±2.3
>11	112	109	97.3±1.6

TABLE X

INTRADERMAL TUBERCULIN TESTS IN 237 BCG-VACCINATED CHILDREN FROM 1 TO 10 YEARS OF AGE. COMPARISON BETWEEN 1.0 MG. OF COMMERCIAL TUBERCULIN AND EQUIVALENT AMOUNT ("1.0" MG.) OF BCG TUBERCULIN. IN EACH OF CASES TEST WAS FIRST TO BE MADE AFTER VACCINATION

Number of weeks after vaccination	Total number of children tested with tuberculin	Positive to 1.0 mg. of commercial tuberculin		Positive to "1.0" mg. of BCG tuberculin	
		Numbers	Percentage rates P±E(P)	Numbers	Percentage rates P±E(P)
3	28	3	10.7±5.9	21	75.0±8.2
4	26	14	53.8±9.7	23	88.5±6.2
5	54	35	64.8±6.5	50	92.6±3.5
6	57	52	91.2±3.8	56	98.2±1.9
7	32	28	87.5±5.7	32	100.0
8	15	14	93.3	15	100.0
9–20	25	24	96.0	25	100.0

reaction was negative to BCG tuberculin in 41 cases (8.3%), and to commercial tuberculin in 208 cases (42.4%). The cases with a positive reaction to commercial tuberculin were also positive to BCG tuberculin.

Of the 41 cases which in the first tests failed to react to either type of tuberculin, 31 were found to be positive on repeated testing. Four children were withdrawn from further examination. Six cases remained negative to both types of tuberculin and were therefore revaccinated after 13, 14, 18, 19 and 20 weeks respectively.

Five of the 167 cases which in the first tests had reacted to BCG tuberculin, but not to commercial tuberculin, were withdrawn from further testing. In all the 162 retested cases the reaction to commercial tuberculin was positive.

The differences between the percentage rates of positive reactions to BCG tuberculin and to commercial tuberculin were statistically significant for all the times investigated between 5 and 11 weeks after BCG vaccination. The BCG tuberculin thus proved superior to commercial tuberculin in the tests performed within this period after vaccination.

The satisfactory results of the BCG tuberculin as demonstrated in the foregoing series (Table VIII) are supported by the data given in Table IX pertaining to an investigation with a far larger number of infants, where BCG tuberculin only was used for testing. The percentage rates for reactions to BCG tuberculin obtained from this series are in good agreement with the corresponding figures in Table VIII.

It is seen from Table X that in the first tests there was a negative reaction to BCG tuberculin in 15 cases (6.3%), and to commercial tuberculin in 67 cases (28.3%). All the cases with a positive reaction to commercial tuberculin were also positive to BCG tuberculin.

Of the 15 cases which in the first tuberculin tests had displayed negative reactions to either type of tuberculin, 13 were found to be positive on subsequent testing, whereas two were withdrawn from further examination. Of the 52 children reacting to BCG tuberculin but not to commercial tuberculin, the examination could not be continued in five. In the 47 retested cases the reaction was consistently positive.

Statistical evaluation of the figures in Table X reveals that the differences between the percentage rates of positive reaction to BCG tuberculin and to commercial tuberculin are significant as regards the examinations made three, four and five weeks after vaccination. Thus in these age groups as well (1 to 10 years) the BCG tuberculin proved superior to commercial tuberculin in the tests performed comparatively shortly after BCG vaccination.

The development of the sensitiveness to tuberculin in the vaccinated children is illustrated by Fig. 4.

Discussion

Careful evaluation of the strength of the tuberculins, in the present case of commercial tuberculin and BCG tuberculin, is indispensable for a comparison between them. The accuracy of the titration method used was satisfactory. To make the comparison as valid as possible, additional precautions were adopted in the principal experiments with animals (Table I) and tests on children (Tables VIII and X). Thus, of the commercial tuberculin, that particular batch which served for evaluation of the BCG tuberculin to be injected was used in the aforementioned experimental series. Further, in the animal experiments the tuberculins were administered in two dosages, i.e., 1.0 and 0.5 mg. of

the commercial tuberculin as well as equivalent amounts of the BCG tuberculin. Moreover, the series were both homogeneous and sufficiently large, the utmost care was exercised as to the procedure in each individual case, and the same technic was used

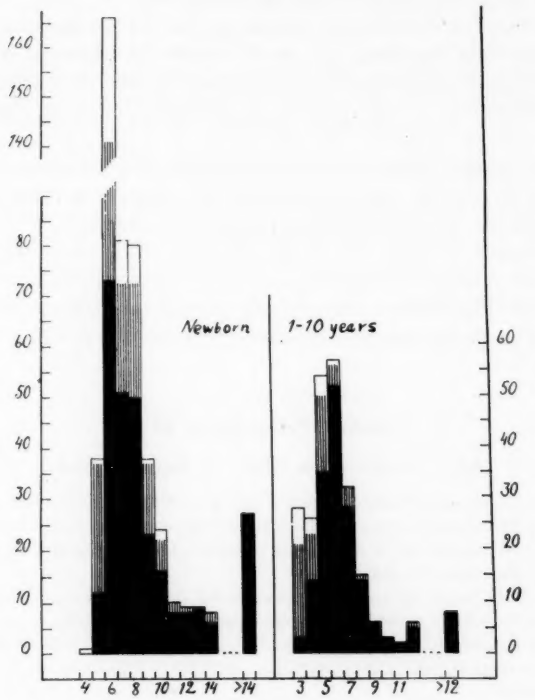

FIG. 4. Incidence of tuberculin sensitiveness in BCG-vaccinated newborn and older children. In all cases the test was the first to be made after vaccination. Comparison between commercial tuberculin and BCG tuberculin. Data taken from Tables VIII and X. The figures on the ordinate indicate the total number of children examined and the proportion of these in which positive reactions were present. The figures on the abscissa indicate the number of weeks after BCG vaccination. The following symbols are used:

□ = Total no. of cases examined

▨ = Positive to "1.0" mg. of BCG tuberculin

■ = Positive to both "1.0" mg. of BCG tuberculin and 1.0 mg. of commercial tuberculin

throughout the entire investigation. Consequently, the considerable difference between commercial tuberculin and BCG tuberculin, which was shown in these tests on children and animals, must be attributed to a qualitative difference in the two types of tuberculin. The question of the actual nature of this difference must, however, at present be left open.

SUMMARY

BCG tuberculin is prepared from BCG cultures grown as a matter of routine on Sauton's medium to obtain Calmette's vaccine. The BCG organisms are allowed to grow for 11 to 12 days prior to the preparation of the tuberculin.

In intradermal tests in BCG-infected guinea pigs this BCG tuberculin causes reactions at an earlier stage than equivalent amounts of commercial tuberculin. In those animals in which initially positive reactions had been caused by only BCG tuberculin, reactions to commercial tuberculin are also obtained in the majority of cases after a further few weeks.

In guinea pigs infected with a virulent strain of the tubercle bacillus no difference can be demonstrated between the two types of tuberculin. Already in the first tests reactions are equally frequent to commercial tuberculin and to BCG tuberculin.

In BCG-vaccinated newborn and older children, BCG tuberculin injected intradermally provokes reactions considerably more often than equivalent amounts of commercial tuberculin. The children sensitive only to BCG tuberculin in the first test after vaccination are subsequently sensitized to commercial tuberculin as well.

SPANISH ABSTRACT

Estudios Tuberculinos BCG

Una Investigación Clínica y Experimental

Se da un informe sobre experimentos llevados a cabo para obtener, con la ayuda de una tuberculina especial, un ensayo Mantoux positivo en infantes vacunados con vacuna Calmette en un período más temprano de lo que es posible con la tuberculina comercial. Los experimentos clínicos fueron suplementados con los experimentos en cobayos.

La tuberculina BCG que se usó en los experimentos fué preparada de cantidades de medio Sauton en las cuales el esfuerzo BCG se había dejado crecer por 10 u 11 días para la producción de rutina de la vacuna BCG. Después de los ensayos de esterilidad se calculó la potencia de la tuberculina BCG mediante titulación contra la tuberculina comercial en los cobayos infectados con un esfuerzo virulento del baccilo tuberculoso.

Subsecuentemente se comparó la tuberculina BCG con la tuberculina comercial, usando por todo 118 cobayos infectados con vacuna BCG. De cualquiera de los tipos de tuberculina, 1.0 y 0.5 mg. respectivamente fué inyectado en el cuero dorsal de los animales 6, 7, 8, 9, 11 y 13 semanas después de la infección con vacuna BCG. Las reacciones evocadas por la tuberculina BCG correspondieron en apariencia con las reacciones de tuberculina ordinaria. 121 cobayos infectados con baccilo tuberculoso virulento fueron usados para los controles. Estos animales fueron inyectados con tuberculina BCG y tuberculina comercial en la misma manera y al mismo tiempo que los animales infectados con organismos BCG.

El resultado de los experimentos fué que en los cobayos infectados con BCG, la tuberculina BCG evocó reacciones tuberculinas positivas en un período más temprano que las cantidades equivalentes de tuberculina comercial evocaron. Seis semanas después de la infección 74.4% y 44.6% fueron positivas a 1.0 y 0.5 mg. tuberculina BCG respectivamente, contra 9.1% y 0% respectivamente a dosis correspondientes de tuberculina comercial. Once semanas después de la infección la proporción era 90.4% y 66.0% respectivamente, contra 9.1% y 23.4% respectivamente. Los cobayos infectados con el baccilo tuberculoso virulento no mostraron diferencia en las reacciones de los tipos de tuberculina. En aquellos cobayos infectados con BCG, en los cuales al principio solamente la tuberculina BCG había evocado reacciones positivas, unas dos semanas más tarde en la proporción mayor de instancias se observaron respuestas aún a la tuberculina comercial, lo que tiende a demostrar que la reacción de la tuberculina BCG es específica.

Se comparó la tuberculina BCG con la tuberculina comercial en niños vacunados con organismos BCG. Esto se hizo, por un lado, con 491 infantes vacunados durante la primera semana de vida; y por otro lado, con 237 niños de 1 a 10 años de edad.

En los infantes los resultados fueron en su mayor parte idénticos a los que se obtuvieron en los experimentos con los animales-en ensayos anteriores, siendo las respuestas considerablemente más frecuentes con tuberculina BCG que con tuberculina comercial—una diferencia que disminuyó gradualmente. De esta manera, seis semanas después de la vacuna 84.9% respondieron a la tuberculina BCG, pero solamente 44% a la tuberculina comercial. Después de 11 semanas la proporción fué 100% y 94.3% respectivamente. En otra serie suplementaria comprendiendo 810 infantes vacunados durante la primera semana de vida, las cifras fueron casi idénticas. En niños de 1 a 10 años de edad, en ensayos hechos tres, cuatro, y cinco semanas después de la vacuna, la tuberculina BCG evocó respuestas considerablemente más amenudo que la tuberculina comercial. Por ejemplo, tres semanas después de la vacuna 75.0% respondió a la tuberculina BCG, pero sólo 10.7% a la tuberculina comercial. Subsecuentemente esta diferencia disminuyó por grados.

En la re-examinación de los niños, que al principio respondieron solamente a la tuberculina BCG, se encontró que se habían vuelto positivos también a la tuberculina comercial. Esta experiencia demuestra que la reacción a la tuberculina BCG es específica.

Al valorar la vacuna Calmette, la tuberculina BCG parece ser preferible a la tuberculina comercial. Esto es verdad particularmente en la vacuna de los recién-nacidos e infantes.

Sachsska Barnsjukhuset

ACUTE SEROUS MENINGITIS AND ENCEPHALITIS COMPLICATING SCARLET FEVER

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CENTRAL nervous system involvement in the course of scarlet fever has been considered to be extremely rare.[1] When major neurologic complications have been encountered, their principal incidence has been recognized to take the form of an acute purulent meningitis caused by the beta Str. hemolyticus.[2] While acute aseptic inflammation, in the clinical forms of both encephalitis and serous meningitis, has been recognized for many years, past reports with few exceptions have included only isolated instances of these infections.

During the past eight years we have encountered 24 patients with acute serous meningitis and one with acute encephalitis that have occurred during the course of scarlet fever. The purpose of the present paper is to report the findings in these patients, to call attention to the frequency with which acute serous meningitis occurs during scarlet fever, and to attempt to differentiate the clinical syndrome produced by this condition from that produced by encephalitis.

HISTORICAL REVIEW

Encephalitis complicating scarlet fever has been known at least since the early 19th century. In 1837 Baudelocque[3] reported two cases of meningoencephalitis occurring in the course of scarlet fever, and in 1841 Cornell[4] wrote "An Essay on the Nature and Treatment of the Form of Scarlatina Connected with Cerebral Symptoms." Since that time there have been reports of this complication by a number of authors. More recently Top and Gordon[2] encountered 23 instances of encephalitis in 17,311 patients with scarlet fever, and Stroe and Banu[5] encountered 13 such patients among 10,200. Gordon[6] reported five cases of postscarlet encephalitis among 158 cases of encephalitis treated in a seven year period.

The occurrence of an acute serous meningitis during the course of scarlet fever has been recognized much more recently. The earliest true case found was reported in 1905 by Dufour and Giroux.[7] They reported a man aged 23 years with severe scarlet fever and a constant headache. He developed a stiff neck. A spinal tap yielded a clear fluid containing an excess of lymphocytes. The headache was relieved by the puncture and the patient had an uneventful convalescence. They also described two other patients with meningoencephalitis. In the discussion of this paper, Dopter[8] reported that he had performed lumbar punctures on 14 patients with scarlet fever. In five cases with general nervous symptoms there were a few lymphocytes. In seven patients there was no reaction, but two patients with a stiff neck and signs of meningeal irritation had more frequent lymphocytes, 20 to 30 per field in the centrifuged sediment of the spinal fluid.

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From 1905 to 1940 there were only occasional reports of serous meningitis complicating scarlet fever, all appearing in the European literature. Lasson and Bang[9] reported 20 cases of aseptic central nervous system complications among 9,826 cases of scarlet fever. Of these patients, four had encephalitis, ten had a lymphocytic meningitis associated with evidence of meningeal irritation, and six had a lymphocytic pleocytosis spinalis without clinical evidence of meningitis. It was thought that the three clinical varieties of central nervous system involvement represented differences of degree of severity rather than qualitative differences in the type of involvement. Nielsen[10] reported six patients with an acute serous meningitis, five of them with an associated polyarthritis. Sweet and Lepper[11] have reported 11 of the 24 patients to be summarized in this report. Melin[12] reviewed the literature and reported 23 cases of central nervous system complications occurring among 18,426 cases of scarlet fever. Of these, nine were of purulent meningitis, 12 were of serous meningitis, and two of encephalitis. Melin felt that 11 of his 12 cases of serous meningitis were associated with otitis or rhinitis in the patient.

Case Reports

The first 11 of these patients have been presented in detail elsewhere.[11] The following four patients give a representative picture of the clinical syndrome and its most frequent variations:

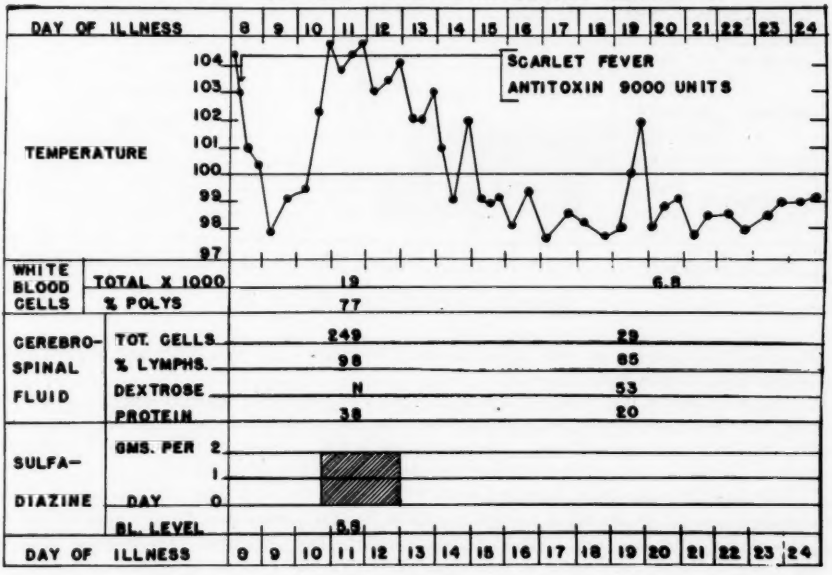

Chart I. Clinical chart of T. B., Case 14.

Case #14 (Chart I), T. B., a Negro female aged 5 yr., was admitted one week after she had developed abdominal pain, fever and sore throat. There was no vomiting. Two days before admission she had developed a rash. History was otherwise irrelevant.

She was acutely ill with fever 40.2°C. and moderately dehydrated. There was a fine erythematous rash on the arms, chest and legs. Tongue, palate and pharynx were characteristic of scarlet fever.

The patient was given 9,000 units of scarlet fever antitoxin on admission, and was given supportive care. Her temperature dropped sharply to normal and on the following day the rash had faded. Temperature remained normal for approximately 30 hours, then rose to 40.4°C. Examination at that time revealed a severe pharyngitis and tonsillitis, for which sulfadiazine was prescribed. The following day, the 11th day of illness, the temperature was still elevated. There was slight but definite stiffness of the neck, and Kernig sign was positive. A spinal tap was done. The spinal fluid contained 249 cells, 98% lymphocytes, a normal amount of dextrose and protein 38 mg./100 cc. fluid. Culture of the fluid was negative, and no organisms could be demonstrated on direct smear of the sediment. WBC count 19 thousand with 77% polymorphonuclear neutrophiles.

When a diagnosis of serous meningitis was made sulfadiazine was discontinued. The temperature declined progressively and became normal on the 15th day. On the 19th day the spinal fluid contained

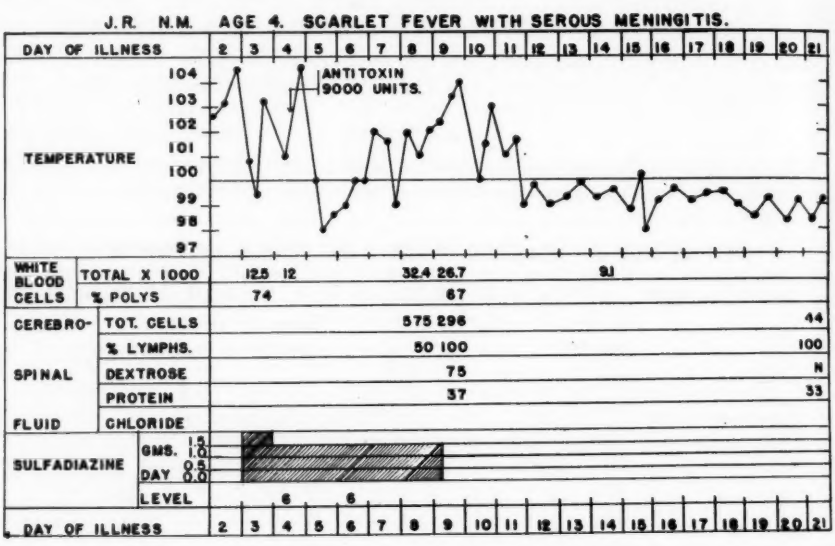

CHART II. Clinical chart of J. R., Case 19.

29 cells, 85% lymphocytes, with normal chemical constituents. She was discharged in good health 24 days after the onset of her illness.

Case #19 (Chart II), J. R., a Negro male aged 4 yr., developed an upper respiratory infection four days before admission. The day before entry he developed fever, sore throat, and later a rash. The child was moderately ill with a temperature of 38.9°C., a pulse of 120/min., and respirations 22/min. He had a rash, tongue and throat that were characteristic of scarlet fever.

The patient's temperature fluctuated from 37.7 to 40.4°C. for 3 days. On the second day he developed cervical lymphadenitis for which sulfadiazine was administered. On the third day he was given scarlet fever antitoxin, 9,000 units intramuscularly. His temperature then dropped to normal for about 40 hours, after which it rose again to 39.4°C. The evidence of acute scarlet fever had subsided, though cervical lymphadenitis was still present. On the seventh day of illness he complained of headache. A spinal tap revealed a marked pleocytosis, with 575 cells/cmm. of which 50% were lymphocytes. The next day there was a lesser, but still marked, pleocytosis, with all the cells being lymphocytes. The protein and dextrose were normal. No bacteria could be demonstrated by either direct smear or culture of the spinal fluid. Sulfonamides were discontinued at the height of the fever, which gradually subsided. The child was discharged improved after 23 days in the hospital, though his spinal fluid had contained 44 lymphocytes/cmm. on the 21st day.

Case #24 (Chart III), C. B., a white male aged 12 yr., developed a "cold" one week before

admission. Three days before admission he developed anorexia and vomited. He was given a laxative, with resultant diarrhea. The day before entry he developed a sore throat, a swollen gland in the neck and a faint rash. The day of admission the patient's rash became much more pronounced, and he complained of a stiff neck. Family and past histories were noncontributory.

Examination revealed a toxic but well-oriented boy of 12 years. His skin, tongue, and pharynx were characteristic of scarlet fever. There was a slight but definite nuchal rigidity. Kernig sign was positive. Tendon reflexes were within normal limits.

A spinal tap on admission revealed 16 cells/cmm. but no other abnormality. The patient was given 18,000 units of scarlet fever antitoxin and supportive therapy. His temperature reached normal within 24 hours, remained normal for one day, then rose to 38.9°C. on the third day in the hospital,

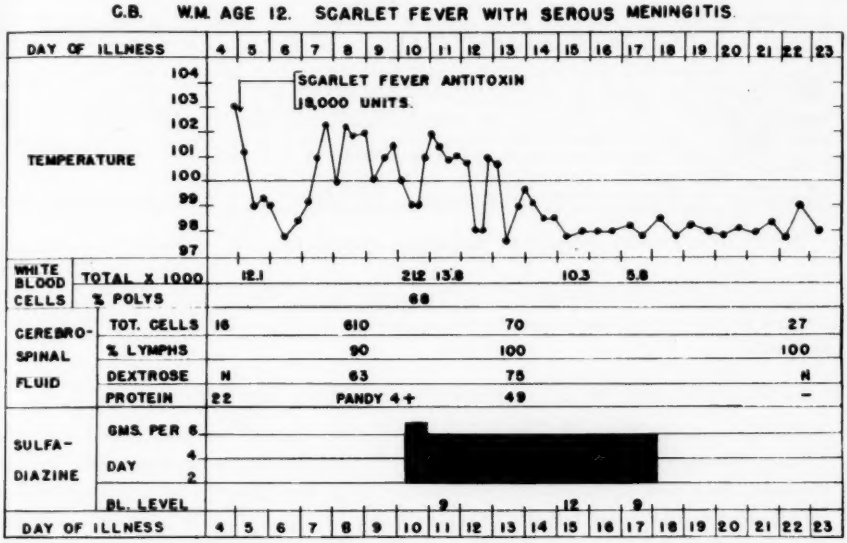
C.B. W.M. AGE 12. SCARLET FEVER WITH SEROUS MENINGITIS.
DAY OF ILLNESS
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
SCARLET FEVER ANTITOXIN 18,000 UNITS.
TEMPERATURE
104 103 102 101 100 99 98 97
WHITE BLOOD CELLS
TOTAL X 1000
12.1 21.2 13.8 10.3 5.8
% POLYS
68
CEREBRO-SPINAL FLUID
TOT. CELLS
16 610 70 27
% LYMPHS
90 100 100
DEXTROSE
N 63 75 N
PROTEIN
22 PANDY 4+ 49 -
SULFA-DIAZINE
GMS. PER 6
4
DAY
2
BL. LEVEL
9 12 9
DAY OF ILLNESS
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23

CHART III. Clinical chart of C. B., Case 24.

the seventh day of scarlet fever. He complained of a severe headache, but showed no evidence of meningeal irritation. A repeat spinal tap revealed a fluid containing 610 cells/cmm., of which 90% were lymphocytes, dextrose 63 mg./100 cc., and a considerable increase of globulin as measured by the Pandy test. Bacteriologic smears and cultures failed to demonstrate organisms. Temperature and headache persisted for three days. At that time he presented evidence of an early catarrhal otitis media. He was given sulfadiazine for the otitis media, which subsided promptly. Thereafter he made an uneventful recovery and was discharged on the 23rd day after onset. He was normal when seen three years after discharge.

Case #12 (Chart IV), D. A., a Negro male aged 5 yr., injured his hand five days before admission. Two days later he became feverish. The lesion on the hand contained pus and there were red streaks up the arm. The following day he developed a generalized scarlatiniform rash. The history was otherwise irrelevant.

He was toxic with a temperature of 37.7°C. There was a characteristic scarlatiniform rash over the body. The tongue, palate, tonsils and pharynx were characteristic of scarlet fever. There was a pustular lesion at the base of the right thumb. Culture made from this lesion grew beta Str. hemolyticus.

He was given two doses of penicillin X, 100,000 units on the 4th day of illness, and 200,000, units on the 5th day. Hot soaks were applied to the hand. The rash faded rapidly, and the patient's general condition was quite satisfactory until the 17th day when he developed a slight fever. On the

21st day the temperature rose to 39.4°C. Beta Str. hemolyticus was recovered from a throat culture. The next day the patient vomited and complained of abdominal pain. On the 23rd day there were signs of meningeal irritation and a spinal tap was done. This showed an opalescent fluid containing 1.2 thousand cells, all lymphocytes, a normal dextrose content and protein 52 mg./100 cc. fluid. No organisms could be demonstrated by bacteriologic smears and cultures. Because of the positive throat cultures he was given penicillin X in four daily doses of 100,000 units each.

The temperature subsided within four days after the initial spinal tap. Subsequent taps showed a

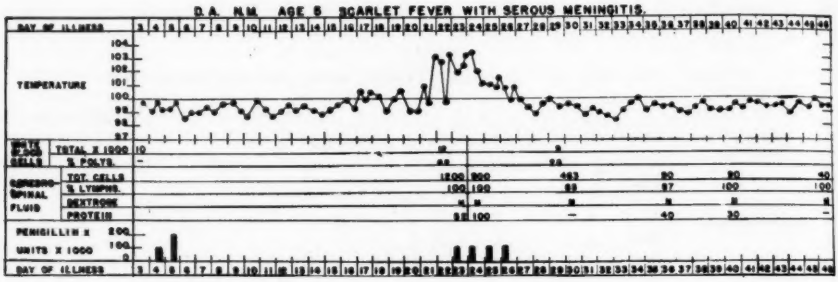

CHART IV. Clinical chart of D. A., Case 12.

progressively lesser abnormality in the spinal fluid until it became normal on the 58th day, 25 days after the first spinal fluid examination. He was in excellent condition when last seen, 31 months after discharge.

CLINICAL FEATURES OF ACUTE SEROUS MENINGITIS COMPLICATING SCARLET FEVER

The 24 patients included in this report were seen in the Isolation Pavilion of the Gallinger Municipal Hospital between January 1, 1939, and December 31, 1946. During this time there were 2,490 patients with scarlet fever. The incidence of this complication and its relation to scarlet fever is shown in Table I. Our experience in recognizing this disease parallels that of Lasson and Bang.[9] In 1939 the complication was not recognized.

TABLE I

INCIDENCE OF SEROUS MENINGITIS IN SCARLET FEVER

Year	Number of cases of Scarlet Fever	Number of cases of Serous Meningitis	Ratio of Meningitis to Scarlet Fever
1939	229	0	—
1940	342	1	1:342
1941	318	2	1:159
1942	304	3	1:101
1943	316	7	1: 45
1944	383	5	1: 75
1945	297	4	1: 74
1946	139	0	—
1947	162	2	1: 69
1942–47	1601	21	1: 76
Total	2490	24	1:104

In 1940 one patient, and in 1941 two patients, were sufficiently similar to be recognized. In 1942 there were three patients so strikingly similar to the previous three that we became interested in the condition. Since that time we have encountered 21 instances of acute serous meningitis among 1,601 patients with scarlet fever (1.3%). This incidence

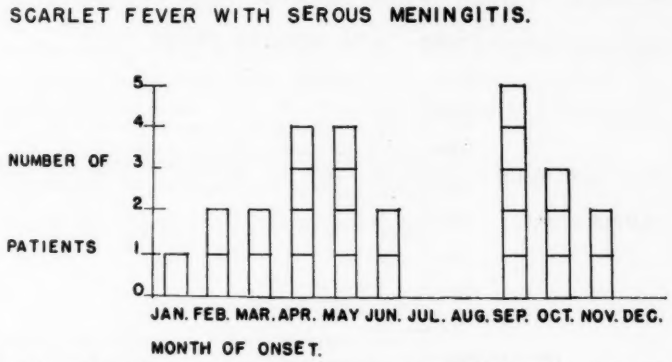

CHART V. Seasonal incidence of 24 cases of acute serous meningitis complicating scarlet fever.

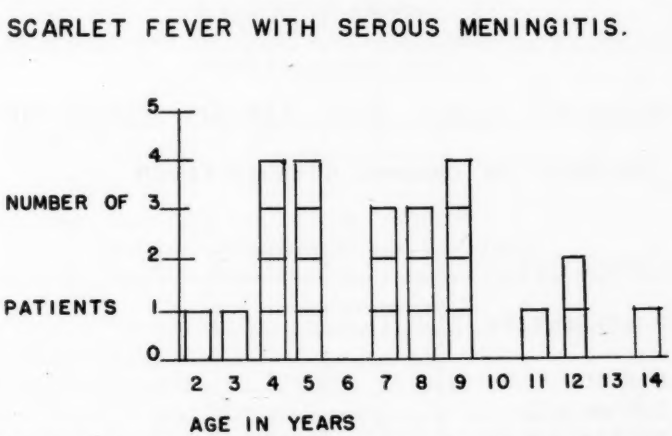

CHART VI. Age incidence of 24 patients with acute serous meningitis complicating scarlet fever.

is higher than the 0.7 to 0.8%, recorded by Lasson and Bang[9] in their year of highest frequency.

The seasonal incidence of this complication (Chart V), parallels reasonably well that of scarlet fever. The paucity of cases in December and January may well be explained by chance in a small group of patients. The higher incidence in September is accounted for by the fact that the three children who aroused interest in this condition had their onset of scarlet fever late in that month.

The age incidence is shown in Chart VI. The principle occurrence is between the ages of 4 and 9 years, with a span of from 2 to 14 years. The first case in an adult has been reported by Dufour and Giroux.[7]

The attack of scarlet fever which led to a complication of serous meningitis was,

by the modern American concepts, moderately severe to severe. The maximum recorded temperature from the primary meningitis is shown in Chart VII. The temperature reached 39.4° C. or above in 17 of the 24 patients. There is no record of the temperature in

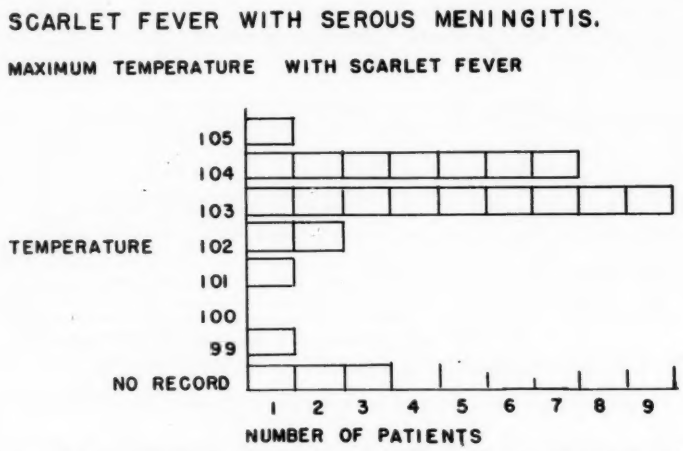

CHART VII. Maximum temperature recorded in 24 patients with scarlet fever who subsequently developed acute serous meningitis.

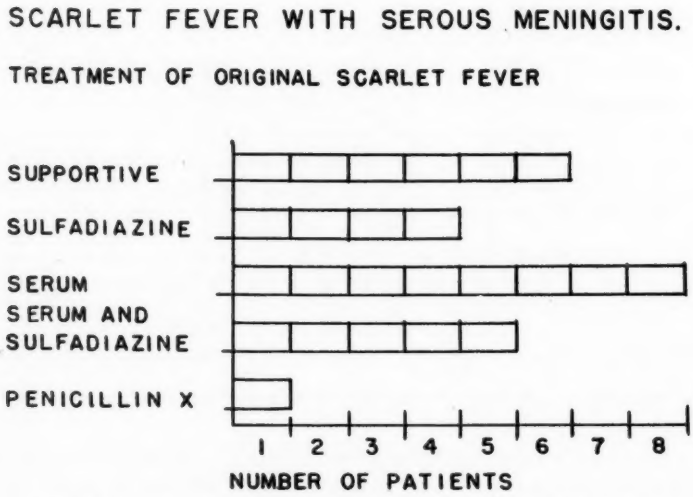

CHART VIII. Treatment given to 24 patients with scarlet fever who developed acute serous meningitis.

three patients who were admitted to the hospital only after the onset of the complicating meningitis. In deference to the severity of the original infection, attempts at specific therapy were made with 18 of these 24 patients (Chart VIII). This included serum alone for 8 patients, serum and sulfonamides for 5, sulfonamides alone for 4, and penicillin

X for 1. This antibiotic was given then in a manner that is now known to be ineffective so that this patient may rightfully be said to have had supportive treatment only. We have had no patients with an acute serous meningitis among approximately 150 patients given adequate penicillin therapy.*

The complicating serous meningitis had its onset relatively early in the course of the scarlet fever, the majority (18) occurring in the second half of the first week (Chart IX) but with a spread of from 4 to 21 days. The meningitis was ushered in with a rise in temperature. Headache and vomiting were prominent symptoms, and the children usually appeared to be toxic. The evidences of meningeal irritation varied con-

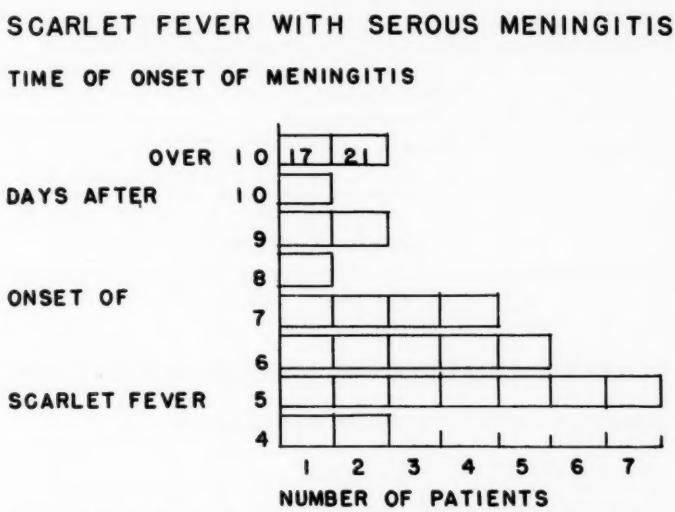

CHART IX. Time of onset of acute serous meningitis in 24 patients with scarlet fever.

siderably. In a few patients there were marked nuchal rigidity, hyperactive tendon reflexes, and a positive Kernig sign. On the other hand, a few patients showed no evidence of meningeal irritation, the diagnostic spinal tap having been done because of the characteristic temperature curve and the absence of evidences of any other suitable explanation of the fever. In the majority of patients there were minimal signs of meningitis, a slightly stiff neck with or without other changes. These were so slight as to be recognized only by a physician who had been alerted to the recognition of the condition.

The temperature rise associated with the meningitis was moderately severe (Chart X), reaching 39.4°C. or over in 20 patients. The characteristic temperature rise was to 39.4 or 40°C. The fever, (Chart XI) lasted from 4 to 9 days, with a duration of 5 to 7 days in 17 patients.

These patients all appear to have recovered from their scarlet fever and meningitis uneventfully and without sequelae. Fourteen of the 24 patients were examined after

* Since this paper was submitted for publication, among 250 patients with scarlet fever adequately treated with penicillin, two have developed an acute serous meningitis.

intervals of from 3 to 8 years following this illness. They ranged in age from 7 to 19 years. Thirteen were making normal progress in school, the other was retarded before he developed scarlet fever. Eight of the 13 children were mentally and socially

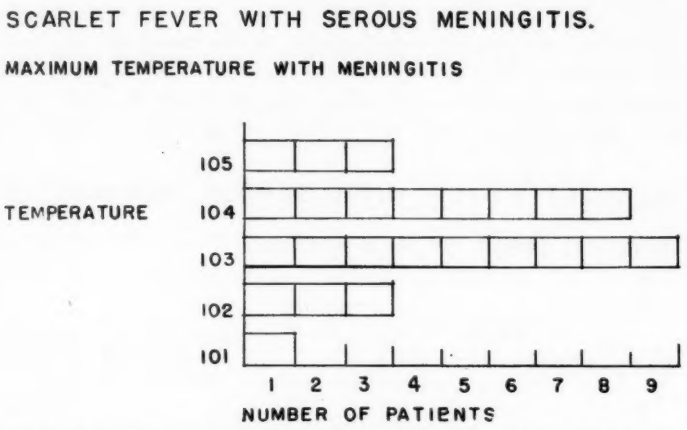

CHART X. Maximum temperature recorded during course of 24 patients with acute serous meningitis complicating scarlet fever.

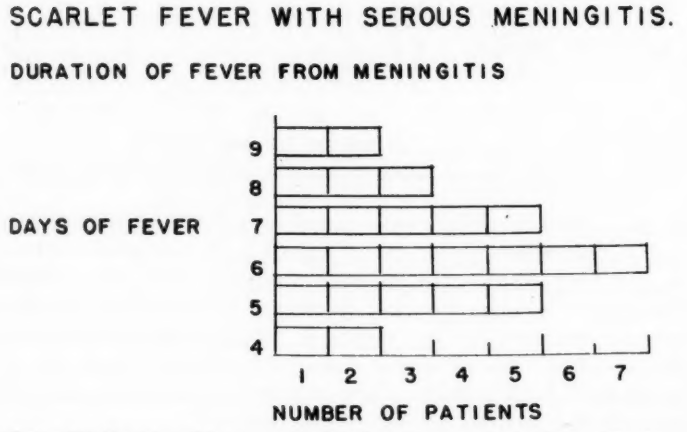

CHART XI. Duration of fever associated with acute serous meningitis complicating scarlet fever in 24 patients.

well adjusted. The other 5 exhibited minor behavior abnormalities more likely from living under conditions of emotional stress than from the scarlet fever or meningitis.

Laboratory findings of the blood and cerebrospinal fluid are given in Table II. The total leucocyte count ranged from 5.75 to 32.4 thousand/cmm. The median count was 16.7 thousand, the average 17.3 thousand. There was a definite increase in polymorphonuclear leucocytes in the differential count in almost all patients. This varied from

52 to 86%, with an average of 70%. When the leucocyte count was high, there was a definite shift to the left.

The cerebrospinal fluid showed changes that were quite characteristic. There was a pleocytosis in all cases, the total count ranging from 32 to 1,200. The median count was 174. There were two counts of more than a thousand cells, seven with less than a hundred. The differential count showed a marked preponderance of lymphocytes. This

TABLE II

LABORATORY FINDINGS IN 24 PATIENTS WITH ACUTE SEROUS MENINGITIS COMPLICATING SCARLET FEVER

Case	Age Yr.	Blood		Cerebrospinal Fluid					
		WBC (Total) thousand	PMN (%)	Total Cells	Lympho-cytes (%)	Sugar (mg./100 cc.)	Protein (mg./100 cc.)	Chloride (mEq./l.)	Days until Normal
1	7	12.7	72	1,100	75	74	—	174	17
2	8	32.0	82	400	80	N*	—	—	No Record
3	4	24.4	63	640	98	74	—	—	26
4	5	26.6	69	200	94	57	100	193	7
5	7	—	—	207	95	55	60	198	6
6	3	—	—	130	90	71	100	179	No Record
7	7	—	—	173	90	76	65	—	9
8	9	17.0	75	32	100	71	65	184	12
9	9	11.8	86	174	97	43	50	189	12
10	8	15.0	—	112	100	63	25	193	17
11	8	31.0	84	56	100	70	—	175	9
12	5	12.0	62	1,200	100	N	100	—	35
13	9	5.7	—	293	100	N	40	212	14
14	5	19.0	77	249	98	N	38	193	9
15	14	12.0	—	50	95	54	100	198	Over 8
16	4	15.2	66	38	88	79	35	180	14
17	9	5.8	—	400	95	60	39	200	12
18	12	16.7	81	160	97	64	60	193	Over 10
19	4	32.4	67	575	50	75	37	—	Over 12
20	11	9.5	64	90	—	N	20	—	Over 10
21	4	10.8	66	38	—	N	12	—	No Record
22	5	22.0	52	105	100	45	78	—	No Record
23	2	11.0	54	44	90	N	100	—	11
24	12	21.0	68	610	90	63	—	—	14

* N = Sugar Normal by Qualitative Test.

was 90% or over in 19 patients. In one instance the initial count recorded only 50% lymphocytes, in two others it was 75 and 80% respectively, while no exact differential count was made on two patients. In the three patients recorded as having less than 90% lymphocytes, subsequent examinations showed a shift to this characteristic finding. The pleocytosis in the spinal fluid was relatively persistent. The last column in Table II, "Days until Normal," records the time interval between the initial spinal tap and the first tap showing less than 30 cells per cmm. This time varied from 6 to 35 days, and was over 10 days in 14 patients. The spinal fluid chemistry was abnormal only in the protein content. There was an elevated protein in most instances, with

only three patients among 19 on whom a quantitative protein determination was made, showing a protein content of 35 mg./100 cc. fluid or less. The maximum total protein was 100 mg./100 cc. There were 11 patients with a total protein of 50 mg./100 cc. or more. There is no significant alteration of the dextrose or chloride content of the spinal fluid.

The etiology of this complication is quite obscure. The clinical picture is strongly suggestive of an infection by a filtrable virus, with the important exception that the leucocyte response in the blood is not characteristic of the majority of infections by these agents. Furthermore, as previously reported,[11] we have sent specimens of cerebrospinal fluid and blood to the National Institute of Health for virus isolation. These specimens have been injected into white mice, hamsters, white rats, cotton rats, guinea pigs, rabbits and one monkey. No virus has been recovered and no significant antibody response has been demonstrated to any virus tested.

There is definite evidence that this condition is not an acute bacterial meningitis. All spinal fluid specimens were cultured on chocolate agar, or other enriched media. In no instance was a pathogenic organism isolated, though common laboratory contaminants were recovered twice. Furthermore, the findings of a normal dextrose content and of a lymphocytic response in the spinal fluid speak strongly against an infection by bacteria. Nor is there any evidence to support the concept that this is a meningitis caused by an infectious process impinging upon the meninges. There was no evidence of a brain abscess, mastoid or sinus abscess, nor any other such infection in any of these patients. The most serious concomitant infection at the time of onset of the meningitis was a pharyngitis, a catarrhal otitis media, or a cervical lymphadenitis.

Encephalitis

The clinical picture of encephalitis complicating scarlet fever, as reported in the literature, is quite polymorphic. Top and Gordon[2] differentiated between an acute toxic encephalitis that occurs early in the course of scarlet fever and usually resolves completely during convalescence, and a true infectious encephalitis that makes its appearance during the period of convalescence from scarlet fever. This latter form often resembles epidemic encephalitis in its clinical manifestations and in its tendency to be followed by disturbing sequelae. The sequelae may be either personality changes or organic nerve damage. Among the 23 cases of encephalitis reported by these authors, 12 were of the early toxic variety and 11 were true encephalitis. Stroe and Banu[5] divided their cases of meningoencephalitis complicating scarlet fever into the psychic form, the choreic form, the choreic and psychic form, encephalitis with phenomena of focal localization, and hemorrhagic encephalomyelitis. Other reports that cite fewer cases of encephalitis mentioned almost every conceivable encephalitic manifestation.

The laboratory findings are equally variable. In most instances there is a lymphocytic pleocytosis in the spinal fluid but, as in our patient, polymorphonuclear leucocytes may predominate. The spinal fluid protein content usually is elevated and the dextrose is normal. The blood leucocyte count may be normal or there may be a considerable leucocytosis.

Our experience with encephalitis in the course of scarlet fever consists of one case.

Case Report

A 4 year old Negro male was admitted on the third day of a relatively mild scarlet fever (Chart XII). He had complained of a fever, sore throat, and a rash for three days. He had been given sulfonamides the day before admission. His past history and family history were not significant. He was well nourished and not acutely ill. His temperature was 36.8°C., pulse 100/min., and respirations 22/min. His blood pressure was 78/40 mm.Hg. His body was covered with a typical scarlatiniform rash, his tongue had a typical "strawberry" appearance, and his pharynx was moderately injected. His WBC count was 7.5 thousand.

The patient was given supportive therapy in the hospital. During the first 10 days of his stay his temperature was essentially normal, and the clinical course was satisfactory. On the 11th hospital day, the 13th day of illness, the patient's temperature rose to 38.3°C., without demonstrable explanation. On the 15th day of illness he appeared to be drowsy and listless, with a fever of 38.1°C., and on the 17th day the temperature rose to 39.5°C. At that time there was moderate right sided cervical

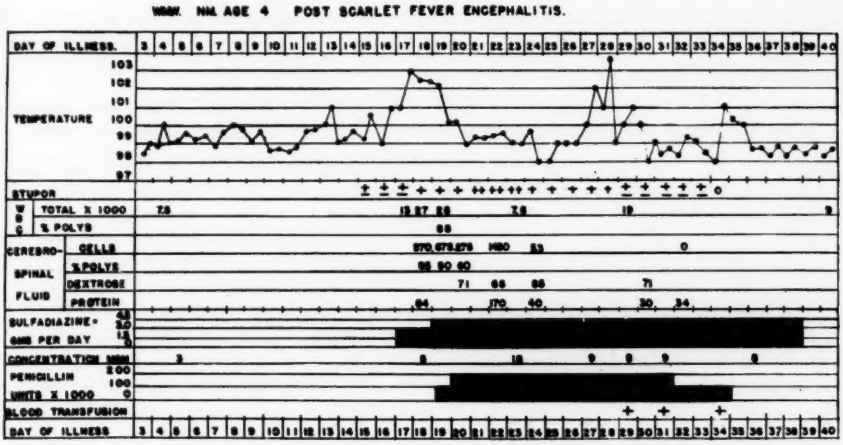

Chart XII. Clinical chart of W. M. W., acute encephalitis complicating scarlet fever.

lymphadenitis; WBC count was 13 thousand. Sulfadiazine was administered in a dose of 3.0 gm./day in divided doses. During the day the patient developed a pain over the left eye, but showed no evidence of meningeal irritation.

The following day (the 18th day of illness) the drowsiness had deepened to a stupor, and there was moderate nuchal rigidity. The WBC count had risen to 27 thousand. A spinal tap was done. The fluid contained 570 cells, 85% polymorphonuclears, protein 84 mg./100 cc. fluid and dextrose 120 mg./100 cc. The sulfonamide dosage was increased to 4.5 gm./day, and penicillin therapy was instituted. He received 100,000 units by continuous drip during the first day, then 200,000 units per day.

A complete neurologic examination on the 20th day of illness showed normal optic fundi, and a paresis of the inferior oblique muscle of the left eye. The left upper extremity was flaccid, the right upper and both lower extremities were spastic. There was a positive Babinski sign on the right. The neck was moderately stiff. The patient was incontinent of urine, and responded to only the most painful stimuli. He refused oral feedings and made no voluntary movements of the extremities. The temperature returned to normal by the 21st day. The pleocytosis in the spinal fluid remained, but dropped to 53 cells on the 24th day (Chart XII). The temperature remained normal from the 21st to 27th day when it again rose to 38.8°C., then to 40.0°. A left otitis media was found to be responsible for this temperature elevation. A myringotomy was done and the temperature returned to normal.

The patient's general condition gradually improved. His stupor lessened and he started taking fluids and food by mouth. The penicillin was discontinued on the 34th day, and sulfadiazine on the

38th day. The peripheral neurologic signs receded slowly. The boy was essentially normal at the time of his discharge on the 51st day after his onset of illness. He had made a complete recovery three years later and showed no mental or physical abnormality.

Differential Diagnosis

In previous reports where these two conditions have been discussed, it has been assumed that the differences between them are quantitative rather than qualitative. In the absence of precise knowledge of the etiology of the two conditions, it is hazardous to assert that there are qualitative differences between them. On purely clinical grounds, however, it seems quite probable that qualitative differences do exist and that the two conditions are etiologically distinct.

This theory is borne out by several observations. Of first importance is that the clinical syndrome of serous meningitis is quite distinct from that of encephalitis. In the former condition the patient, though toxic, is alert and cooperative rather than stuporous or comatose; cranial or peripheral neurologic complications are unknown rather than common, and psychic or neurologic sequelae occur infrequently, if at all. The clinical differences exist with all degrees of severity of the illnesses. As between patients with serous meningitis with and without nuchal rigidity and other evidences of meningeal irritation, the transition is gradual with no sharp line of demarcation. As between serous meningitis and encephalitis, however, there is a clear cut distinction. Even the most severely ill patients with serous meningitis are alert and free from neurologic or psychic manifestations.

The difference in the incidence of the two conditions is of some importance. Serous meningitis has been reported in between 0.7 and 0.8% of patients with scarlet fever by Lasson and Bang[9] in their year of most frequent occurrence. In our series it occurred in 1.0 to 1.3%. On the other hand, Top and Gordon[2] and Stroe and Banu[5] found encephalitis in 0.13% of their patients with scarlet fever. Thus the incidence of serous meningitis, when it is carefully investigated, is found approximately ten times as frequently as is encephalitis.

The outcome of the disease is a third striking clinical difference. Patients with encephalitis often are left with residuals of organic neurologic disorders or of psychologic aberrations. With acute serous meningitis, on the other hand, recovery seems to be immediate and complete, without sequelae of any kind.

Summary

The syndrome of acute serous meningitis complicating scarlet fever has been described. The condition has been found in approximately 1% of patients with scarlet fever. The onset usually is in the second half of the first week of illness. There is a recrudescence of fever with headache, toxemia, meningeal signs which may be minimal or absent, and a lymphocytic pleocytosis in the spinal fluid. The blood shows a polymorphonuclear leucocytosis in most instances. The condition ameliorates rapidly and recovery seems to be complete. The clinical manifestations of this syndrome are quite different from those of encephalitis complicating scarlet fever. The points in differential diagnosis have been outlined.

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SPANISH ABSTRACT

Meningitis Serosa aguda y Encefalitis en Complicación con la Fiebre Escarlatina

Se ha descrito el síndrome de meningitis serosa aguda en complicación con la fiebre escarlatina. La condición se encontró en aproximadamente 1% de los pacientes con fiebre escarlatina. El ataque generalmente ocurre en la segunda mitad de la primera semana de la enfermedad. Hay una recrudescia de fiebre con dolor de cabeza, toxemia, signos meníngeos que pueden ser mínimos o estar ausentes, y una pleocitosis linfocítica en el flúido espinal. La condición mejora rapidamente y el restablecimiento parece ser completo. Las manifestaciones clínicas de este síndrome son completamente diferentes a las de la encefalitis en complicación con la fiebre escarlatina. Se delinean los puntos en la diagnosis diferencial.

19th St. and Massachusetts Ave.

THE EFFECT OF SMALLPOX VACCINATION DURING PREGNANCY ON THE INCIDENCE OF CONGENITAL MALFORMATIONS

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THE importance of environmental factors, and especially of infections, in the causation of anomalous embryos, was pointed out dramatically by Gregg[1] in 1942. He made the observation that a preponderant number of infants with congenital cataract examined by him were offspring of women who had rubella during the first trimester of pregnancy. Other reports have appeared not only in the Australian but also in the British and American literature on the effects of maternal rubella on the newborn offspring. The most extensive studies are those of Swan and his collaborators,[2] who have indicated that other acute infectious diseases occurring in early pregnancy may also influence the development of defects in the newborn babies. The mass vaccination of about five million persons in the period of a month, following an outbreak of variola in New York City in 1947,[3, 4] presented an opportunity to observe the effects of smallpox vaccination during pregnancy on the developing embryo.

METHOD OF STUDY

Two parallel studies were conducted, one in child health stations and the other on the maternity wards of hospitals. The Department of Health of New York City maintains 67 child health stations. Approximately 30 thousand new infants are registered yearly. They are usually brought first to the clinics within three months after birth. A complete physical examination is made by the clinic physician and noted on the child's record. Thereafter, about eight visits are made during the first year of life for such purposes as observation of developmental progress, changes of formula and immunizations. From October 1, 1947 to March 31, 1948 the examinations of all infants registered in the clinics who were born between October 1, 1947 and January 31, 1948 were noted on a special epidemiologic card. Particular note was made of the occurrence of any abnormality. Also noted were the date of birth, date of examination, birth weight, sex and color of the child, age of the mother, whether she was vaccinated successfully, date of last vaccination and whether a recent scar was observed by the examining physician. The cards were collected periodically.

The hospital group of cases came from a parallel study on the maternity services of 11 New York City hospitals.† The cooperation of the respective obstetric and pediatric house staffs was solicited. Epidemiologic cards similar to those of the Department of Health were distributed to these physicians. The results of the routine physical examinations of the newborn infants were entered on these cards within the first two days following birth. The usual procedure was for the obstetric service to record the pertinent information concerning the mother. The card was then transferred to the newborn infant's chart to be completed by the pediatric service.

The cards were collected at routine intervals and analyzed. There was a total of 5,300 full term

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* National Institute of Health Postdoctorate Research Fellow.

† The following hospitals cooperated: Bellevue, City, Metropolitan, Lincoln, Fordham, Kings County, Greenpoint, Cumberland, Coney Island, Queens General and Jewish.

live births in all these hospitals during the period of study. Of these it was possible to obtain completed cards on 2,787. At the end of the study the two sets of cards were compared and duplicates eliminated.

All infants weighing less than 2,500 gm. were considered premature. Only those that were viable and less than three months of fetal age during the vaccination period were included in the study. The fetal age was estimated by the birth weight. Infants under 1,000 gm. were considered to have a fetal age of less than 28 weeks; those between 1,000 and 1,499 gm., of 28 to 31 weeks; those between 1,500 and 1,999 gm., of 31 to 34 weeks and those from 2,000 to 2,400 gm., of 34 to 36 weeks.

The data for deaths from congenital malformation and for stillbirths were obtained from the statistical division of the Health Department.*

The two investigations complemented each other. If babies are examined in the first weeks of life, a larger number of malformations will be seen, since many such infants die in the neonatal period and others visit hospital outpatient clinics rather than health clinics. On the other hand, certain congenital defects which may not be recognizable in the first week of life and only become apparent later will not be recognized on the maternity ward but will be picked up in the child health stations. In these investigations, whenever it was found necessary to re-examine an infant or to obtain further data, either a revisit to the health station was requested or a visit was made to the child's home.

There were 4,172 vaccinated and 2,186 unvaccinated women in the combined study. The distribution by age and color was similar in the two groups.

Results

Congenital Malformations

Table 1 lists the defects found in the combined groups, according to the month of pregnancy when vaccination was performed. There were 31 single or multiple defects in the offspring of the 4,172 vaccinated women and 13 in those of the 2,186 unvaccinated ones. At the bottom of the table are listed three other defects which were found: club foot, inguinal hernia and hydocele, and hemangioma. These are not included in the totals noted above since some doubt existed as to whether they should be considered as congenital defects or as allowable deviations from the normal. In the case of hemangiomas there is some evidence that the factors influencing their causation are not operable until after the first trimester of pregnancy.[5] Totals for each of these defects are therefore given separately. The grand totals, with these defects included, are 68 in the vaccinated group and 30 in the unvaccinated.

It should be pointed out that there is epidemiologic and embryologic evidence that some of the defects noted in the tables are caused by factors operating in the first trimester of pregnancy.[6] These are mongolian idiocy,[7] congenital heart disease[1, 2] and congenital cataract.[1] In the case of the others, the evidence that the defects, if caused by an environmental factor, occur in the first trimester of pregnancy is based on embryologic knowledge only.[8, 9] According to Warkany,[10] the organogenetic period of gestation in man is terminated about the tenth week. Some of the malformations, such as supernumerary and absent digits, absent ear lobes, harelip and cleft palate, might be classified as due to defective genes. However, Warkany[11] considers that the same type of malformations may be due to either genetic or environmental factors. Furthermore, even if defects are genetic, they may be due to environmental influences on the genes.[12]

* Mr. Louis Weiner, Chief of the Statistical Division, made the data available.

Table 2 gives the numbers and rates of congenital defects according to the month of pregnancy when the mother was vaccinated. The hospital and health department groups are tabulated separately. The vaccinated women are divided into those who showed a recent scar of vaccination at the time of examination and those who did not. Since the vaccination period extended from April 7 to May 3, a spread of 26 days, the midpoint of 13 days was used as the beginning of the month. Vaccinated women whose

TABLE 1

CONGENITAL MALFORMATIONS

Combined Groups

Number of Infants	2201				1971				4172				2186			
Malformations	Vaccinated Scar				Vaccinated No Scar				Total Vaccinated				Unvaccinated			
	Mo. of Pregnancy				Mo. of Pregnancy				Mo. of Pregnancy				Mo. of Pregnancy			
	1	2	3	Total	1	2	3	Total	1	2	3	Total	1	2	3	Total
1. Mongolian Idiocy & Congenital Heart															1	1
2. Mongolian Idiocy		1		1						1		1				
3. Congenital Heart			1	1	1		1	2	1		2	3			1	1
4. Congenital Cataract & Congenital Heart	2			2					2			2				
5. Cleft Palate & Hare Lip			1	1	1		3	4	1		4	5	1			1
6. Cleft Palate & Pilonidal Cyst		1		1						1		1				
7. Cleft Palate & Hypospadias													1			1
8. Hypospadias		1	1	2			1	1		1	2	3		1		1
9. Spina Bifida & Meningocele		1		1			1	1		1	1	2				
10. Spina Bifida & Club Feet		1		1						1		1				
11. Spina Bifida & Hydrocele			1	1							1	1				
12. Cerebral Agenesis			1	1							1	1				
13. Microcephaly & Fusion of Eyes and Nose														1		1
14. Hypodevelopment of Mandible							1	1			1	1				
15. Imperforate Anus, Absent Gall Gladder, Malformed Hands															1	1
16. Imperforate Urethra			1	1							1	1				
17. Double Urethra Open	1			1					1			1				
18. Polycystic Kidneys		1		1						1		1				
19. Absent Ear Lobes													1			1
20. Absent Fingers or Toes					2			2	2			2				
21. Supernumerary Digits		1	1	2	2			2	2	1	1	4	1	1	1	3
22. Flail Thumb						1		1		1		1		1		1
23. Atresia of Bowel														1		1
TOTAL	3	7	7	17	6	1	7	14	9	8	14	31	4	5	4	13
24. Club Feet	2	2	4	8	1		1	2	3	2	5	10		2	3	5
TOTAL	5	9	11	25	7	1	8	16	12	10	19	41	4	7	7	18
25. Hydrocele & Inguinal Hernia	5	2	2	9	2	1	1	4	7	3	3	13		1	5	6
TOTAL	10	11	13	34	9	2	9	20	19	13	22	54	4	8	12	24
26. Hemangioma	3		7	10		2	2	4	3	2	9	14	1	1	4	6
TOTAL	13	11	20	44	9	4	11	24	22	15	31	68	5	9	16	30

full term babies were born between December 20 and January 19 were considered to have been in the first month of pregnancy at the time of vaccination; those whose babies were born between November 20 and December 19 were considered to have been in the second month of pregnancy at that time, and those delivering between October 20 to November 19 in the third month.

There were 1,853 vaccinated and 934 unvaccinated women in the hospital group, and the number of infants with congenital defects born to those women were 23 and 12,

TABLE 2

CONGENITAL MALFORMATIONS

	Hospital Group												Health Department Group											
	Vaccinated Scar			Vaccinated No Scar			Total Vaccinated			Total Unvaccinated			Vaccinated Scar			Vaccinated No Scar			Total Vaccinated			Total Unvaccinated		
Month of Pregnancy	No.	Defect	%	No.	Defect	%	No.	Defect	%	No.	Defect	%	No.	Defect	%	No.	Defect	%	No.	Defect	%	No.	Defect	%
1	293	1	.34	198	5	2.52	491	6	1.22	209	3	1.44	499	2	.40	409	1	.24	908	3	.33	257	1	.39
2	325	5	1.54	292	0	0.0	617	5	.81	254	4	1.63	451	2	.44	486	1	.21	937	3	.32	477	1	.21
3	378	5	1.32	367	5	1.36	745	10	1.34	480	3	0.62	594	2	.34	483	2	.41	1077	4	.37	744	1	.13
Total	996	11	1.10	857	10	1.18	1853	21	1.13	934	10	1.08	1544	6	.39	1378	4	.29	2922	10	.34	1478	3	.20
Plus Club Feet	996	12	1.20	857	11	1.28	1853	23	1.24	934	12	1.28	1544	13	.84	1378	5	.36	2922	18	.62	1478	6	.41
Plus Hydrocele and Inguinal Hernia	996	12	1.20	857	11	1.28	1853	23	1.24	934	12	1.28	1544	22	1.42	1378	10	.73	2922	31	1.06	1478	12	.81
Plus Hemangioma	996	12	1.20	857	11	1.28	1853	23	1.24	934	12	1.28	1544	32	2.06	1378	13	.94	2922	45	1.54	1478	18	1.22

TABLE 3

CONGENITAL MALFORMATIONS—COMBINED GROUPS

	Vaccinated Scar			Vaccinated No Scar			Total Vaccinated			Unvaccinated		
Month of Pregnancy	No.	Defect	%	No.	Defect	%	No.	Defect	%	No.	Defect	%
1	695	3	0.43	549	6	1.09	1244	9	0.72	427	4	0.93
2	644	7	1.09	666	1	0.15	1310	8	0.61	635	5	0.79
3	862	7	0.81	756	7	0.93	1618	14	0.87	1124	4	0.35
TOTAL	2201	17	0.77	1971	14	0.71	4172	31	0.74	2186	13	0.59
Plus Club Feet	2201	25	1.14	1971	16	0.81	4172	41	0.98	2186	18	0.82
Plus Hydrocele	2201	32	1.45	1971	20	1.01	4172	52	1.25	2186	23	1.05
Plus Inguinal Hernia	2201	34	1.54	1971	20	1.01	4172	54	1.29	2186	24	1.10
Plus Hemangioma	2201	44	2.00	1971	24	1.22	4172	68	1.63	2186	30	1.37

respectively. In the health department group 2,922 vaccinated and 1,478 unvaccinated women gave birth to 45 and 18 defective infants, respectively. The percentage rates for congenital anomalies were, therefore, 1.24 in the vaccinated and 1.28 in the unvaccinated of the hospital group and 1.54 and 1.22, respectively, of the health department group. There is no statistical difference between the rates for vaccinated and unvaccinated in either group, nor is there any statistical significance when comparisons are made in any of the three months.

In Table 3 the two groups have been combined and duplicate cards eliminated. The total number of vaccinated women was 4,172 and these gave birth to 68 malformed infants, a percentage rate of 1.63. There were 2,186 unvaccinated women, who gave birth to 30 defective infants, a rate of 1.37%. Here again there is no statistical significance between the two groups.

The inclusion of the women who showed no vaccination scars in the vaccinated group may produce a bias. Actually, many of them may have had no takes and should be properly included in the unvaccinated group. Since it was not possible to separate those who might have had an immune reaction from those who had no take, they were all included in the vaccinated group. If we compare only the group that showed a vaccination scar with the controls we still get no difference of statistical significance.

Premature Infants

One of the effects of prenatal injury might be that of premature birth. Therefore, the incidence of premature births was compared in the vaccinated and unvaccinated groups. It should be pointed out that in each of the months under consideration only those prematures were included that were old enough to have been viable and not more than three months of fetal age during the vaccination period. It will be seen from Table 4 that 277 premature infants, or 6.6%, were born to the 4,172 vaccinated women as contrasted with 157 prematures, or 7.2%, born to the 2,186 unvaccinated women. The rates of prematurity for each of the three months for the vaccinated and unvaccinated groups are given in the table. There is no significant difference between the two in any of the months, nor between the two totals.

Since some of these prematures might have been born prior to October 20, the number of all prematures registered in the health stations who were born between September 1 and October 19, and who were viable and less than three months of fetal age during the vaccination period, were added. With these additions, the total number of prematures born to the vaccinated women was 343, or 8.2%, and the total born to the unvaccinated women was 185, or 8.4%. These rates correspond to the premature rate for the city of New York. During 1947 there were 171,174 births, and 13,782 of these were premature, a rate of 8.0%.

Deaths from Congenital Malformations

A comparison was made between the deaths from congenital malformations in New York City during the months of October, November and December 1947 and January 1948 with deaths from similar causes in the same months of the preceding year. Since more than two thirds of the population was vaccinated in 1947, a significant difference in rates might be expected if vaccination in the first trimester of pregnancy had an adverse effect on the unborn infant. Table 5 indicates the number of deaths and the mortality rates per 10,000 live births. There were 259 deaths occurring from congenital

TABLE 4

PREMATURE BIRTHS—COMBINED GROUPS

Month of Pregnancy	Vaccinated Scar			Vaccinated No Scar			Total Vaccinated			Unvaccinated		
	No. of Live Births	No. of Pre-matures	Percent of Pre-matures	No. of Live Births	No. of Pre-matures	Percent of Pre-matures	No. of live Births	No. of Pre-matures	Percent of Pre-matures	No. of Live Births	No. of Pre-matures	Percent of Pre-matures
1	695	56	8.1	549	20	3.6	1244	76	6.1	427	29	6.8
2	644	83	12.9	666	34	5.1	1310	117	8.9	635	54	8.5
3	862	48	5.6	756	36	4.8	1618	84	5.2	1124	74	6.6
Total	2201	187	8.5	1971	90	4.6	4172	277	6.6	2186	157	7.2
Plus Prematures, born Sept. 1-Oct. 19	2251	237	10.5	1987	106	5.3	4238	343	8.1	2214	185	8.4

TABLE 5

INFANT DEATHS AND MORTALITY RATES FROM CONGENITAL MALFORMATIONS, NEW YORK CITY, DURING CERTAIN MONTHS IN 1946, 1947 AND 1948

	Live Births		Deaths from Congenital Malformations		Mortality Rates (per 10,000 live births)	
	1946	1947	1946	1947	1946	1947
October	15,862	13,945	65	64	41.0	45.9
November	14,746	13,034	80	71	54.3	54.5
December	15,508	13,566	71	62	45.8	45.7
	1947	*1948*	*1947*	*1948*	*1947*	*1948*
January	15,324	12,572	74	62	48.3	49.3
Total	61,440	53,117	290	259	47.2	48.8

malformations, a rate of 48.8 per 10,000 live births in the last three months of 1947 and the first month of 1948, and 290 deaths, a rate of 47.2 per 10,000 live births in the same four months of the previous year. There is obviously no significant difference between deaths from congenital malformations in the two periods.

STILLBIRTHS

The same influences that cause malformations in the viable fetus may, if sufficiently severe, cause the death of the embryo before birth. An examination of stillbirth rates in 1947 and a comparison of these with the rates for 1946 is therefore of interest. In New York City a stillbirth is defined as any product of conception except a live birth. For statistical purposes stillbirths are divided into three groups: 1. under 20 weeks' gestation at birth, 2. 20 to 27 weeks' gestation at birth and 3. over 28 weeks' gestation at birth. In Chart 1* the 1947 monthly stillbirth ratios are expressed as percentages of the corresponding 1946 ratios. The line marked 100 represents equality between the 1947 and 1946 ratios. Obviously, if the 1947 ratio is greater than the corresponding ratio for 1946, the bar will extend above the 100 line, while if it is less it will be below the 100 line. It will be noted that the solid bars, which represent the fetuses that may have been alive and less than three months of age during the vaccination period, do not uniformly extend above the 100 line. Of the 15 solid bars, only six showed an increased ratio of 1947 over 1946. One must conclude that there is no indication from this chart that vaccination exerted any influence on the causation of stillbirths.†

* Vivian Pessin, Senior Statistician, New York City Department of Health, suggested the construction of this chart.

† Theoretically, it is more accurate to calculate stillbirth ratios by dividing the number of stillbirths conceived in a given month by the number of live births conceived in the same month. However, the wide range of the stillbirth age groups, the inaccuracy of gestation reporting, and other factors would necessitate the use of so much estimation that it is doubtful whether the results would have any more significance than those given above. An attempt was made to estimate theoretically correct stillbirth ratios for one of the stillbirth age groups; the results were compatible with the conclusions drawn from the data as used.

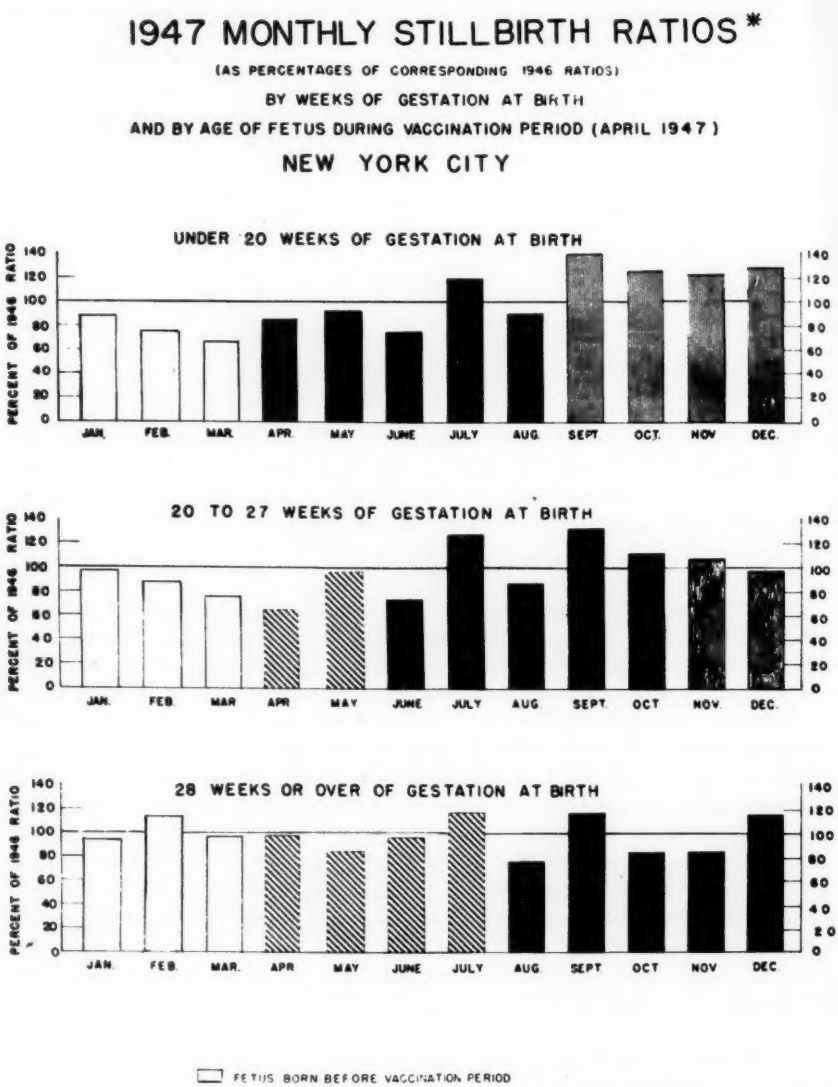
1947 MONTHLY STILLBIRTH RATIOS*
(AS PERCENTAGES OF CORRESPONDING 1946 RATIOS)
BY WEEKS OF GESTATION AT BIRTH
AND BY AGE OF FETUS DURING VACCINATION PERIOD (APRIL 1947)
NEW YORK CITY
UNDER 20 WEEKS OF GESTATION AT BIRTH
20 TO 27 WEEKS OF GESTATION AT BIRTH
28 WEEKS OR OVER OF GESTATION AT BIRTH
PERCENT OF 1946 RATIO
0
20
40
60
80
100
120
140
JAN.
FEB.
MAR.
APR.
MAY
JUNE
JULY
AUG.
SEPT.
OCT.
NOV.
DEC.
FETUS BORN BEFORE VACCINATION PERIOD
FETUS MORE THAN THREE MONTHS OF AGE DURING VACCINATION PERIOD
FETUS MAY HAVE BEEN ALIVE AND LESS THAN THREE MONTHS OF AGE DURING VACCINATION PERIOD
FETUS NOT YET ALIVE DURING VACCINATION PERIOD
* STILLBIRTH RATIO IS THE NUMBER OF STILLBIRTHS PER 1000 LIVE BIRTHS.

CHART I

Comment

The recent studies of Aycock, Gordon and Ingalls have revived interest in the observation of environmental changes that may influence a developing embryo. Such alterations may result in a defective offspring. Some of the early work in this field, such as that of Loeb and Stockard, was experimental and was conducted with the ova of lower animals. Stockard, for instance, caused the eggs of fish to form embryos with cauda bifida by adding lithium salts to their environment.[13] More recently, Warkany,[10] in a series of brilliant experiments, has shown that occurrence of specific malformations in newborn rats can be predicted if the mothers are fed incomplete diets, or diets defective in certain vitamins. Direct experimental work is, of course, not possible in humans. Mall[14] studied human monsters from the anatomic point of view, and attempted to discover the causes underlying their origin. Gordon and Ingalls[6] pointed out that the study in humans should be a combined epidemiologic and teratologic investigation. Observations should be made of accidents, illnesses and other injuries that may occur in the course of pregnancy and the effect of these on the offspring. Such observations should be correlated with the embryologic study of the fetus so as to determine whether the injury could produce the deformity found in the infant at birth if it operated at a particular time of pregnancy. As examples of such correlated studies, they mention mongolism,[7] postrubella defects,[1,2] encephalophthalmic dysplasia,[5] and birth injuries. There is need for information of negative as well as of positive influences. The method used in our investigation is along more classic lines than that proposed by Gordon and Ingalls.[6] In certain respects it gives more accurate information. In the case of communicable diseases it can be readily adopted in any community large enough to yield sufficient data.

Most of the studies of the effect of rubella in the pregnant woman on the development of congenital defects in her offspring, including the original observation of Gregg[1] and the studies of Swan and his collaborators,[2] need confirmation. They are based on the observation of children with defects and the subsequent determination by means of a retrospective history, the accuracy of which is frequently doubtful, whether the mother did or did not have rubella in the first trimester of her pregnancy. There is need for follow-up studies of pregnant women who contract rubella in their pregnancies, and for a comparison of the incidence of malformations in their offspring with that in infants born to an equal number of pregnant women who have not had rubella. Fox and Bortin[15] investigated 22,226 cases of rubella. Among them were 152 married women, of whom 11 were pregnant, nine in the first trimester. One of the 11 babies born subsequently was a stillbirth; the others were normal. Aycock and Ingalls[16] investigated 1,300 cases of reported rubella in Massachusetts and found among them four cases of pregnancy, two in the first trimester, which resulted in the births of three normal and one mentally retarded infant. These findings do not justify the general impression that women who have rubella in the first trimester of pregnancy will necessarily have a defective child.

Vaccinia is a general infection. It has been established by numerous investigations that the virus enters the blood stream and is widely distributed in the tissues.[17] It might, therefore, cause injury to the developing embryo. We have attempted to test the possibility by a statistical evaluation of malformations occurring in the offspring of women vaccinated in the first trimester of pregnancy, the deaths from congenital

deformities in their infants, the occurrence of premature births and relative percentage of stillbirths. The results of this study are of practical importance, since they offer the practicing physicians information on the advisability of vaccinating pregnant women under their care.

It would have been of interest to carry the study through the nine months of pregnancy. This was not done. However, data have been accumulated from the health department clinics to cover the fourth month of pregnancy. They were presented in a preliminary form before the Pediatric Section of the New York Academy of Medicine.[18] The conclusions were not different from those presented here.

The studies were carried on independently by two groups. The health department group included all clinic infants, while the hospital group included infants born on certain maternity services. The data from each group analyzed independently yielded similar results. The combined figures, with duplicates eliminated, also indicated that vaccination of women in the first trimester of pregnancy showed no deleterious effect on the newborn infants in the groups studied.

Conclusions

Following an outbreak of variola in New York City early in 1947, more than five million people were vaccinated. Among these there were observed 4,172 women in the first trimester of pregnancy. They gave birth to 68 children with malformations, an incidence of 1.63%. A control, nonvaccinated group of 2,186 women in the same period of pregnancy, gave birth to 30 malformed infants, an incidence of 1.37%.

The vaccinated group gave birth to 343 premature infants, a rate of 8.2%, while the nonvaccinated group gave birth to 185 prematures, a rate of 8.5%.

Deaths from congenital malformations in New York City during the four months representing the first trimester of pregnancy of the observed women numbered 259, a rate of 48.8 per 10,000 live births. In the corresponding months of the preceding year the number of deaths was 290, a rate of 47.2 per 10,000 live births.

There was no apparent increase in the ratios of stillbirths to total births in 1947, during the months when the stillbirths may have been conceived, over the ratios of the corresponding months of the previous year.

There is no evidence from these studies that smallpox vaccination of women in the first trimester of pregnancy has any deleterious effect on the developing embryo.

Acknowledgment

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SPANISH ABSTRACT

Efecto de la Vacuna contra Viruela durante el Embarazo en la Incidencia de Malformaciones Congénitas

En 1947 más de cinco millones de personas fueron vacunadas en la Ciudad de Nueva York. El virus de la vacuna entra en la sangre durante la inoculación. Como hay prueba de que otras enfermedades infecciosas que ocurren durante el embarazo pueden tener un efecto deletéreo en el reciénnacido, se llevó a cabo un estudio para determinar el efecto de la vacuna durante el embarazo en la incidencia de malformaciones congénitas.

El estudio incluyó, 4,172 mujeres que fueron vacunadas durante el primer trimestre del embarazo, y 2,186 mujeres en el mismo período del embarazo que no fueron vacunadas. Las primeras dieron a luz 1.63% de infantes malforados y las últimas 1.37%. La diferencia no es significativa. El porcentaje de infantes prematuros que les nacieron a las mujeres vacunadas también varió poco del que les nacieron a las mujeres sin vacuna.

Como más de las tres cuartas partes de la población de Nueva York fueron vacunadas en abril 1947, se hizo una comparación mensual de las proporciones de partos muertos con el número total de nacimientos en 1946 y 1947. No hubo aumento en la proporción en aquellos meses cuando los partos muertos podrían haber sido concebidos por las mujeres vacunadas. También se hizo una comparación entre las muertes de malformaciones congénitas en infantes concebidos durante el período de vacuna y muertes similares en el mismo período del año anterior. De nuevo, la diferencia en la proporción no fué significativa.

125 Worth St.

CENTRAL AUTONOMIC DYSFUNCTION WITH DEFECTIVE LACRIMATION

I. Report of Five Cases

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IN THE course of the past 10 years four children have appeared at Babies Hospital with symptoms so puzzling as to defy exact diagnosis yet so similar as to constitute a clinical entity. A fifth patient with the same condition has been studied at The New York Hospital. The common features are: 1. undue reaction to mild anxiety characterized by excessive sweating and salivation, red blotching of the skin and transient but marked arterial hypertension, and 2. constantly diminished production of tears.

Search among textbooks and current literature has failed to reveal a description of a syndrome exactly corresponding to the one described. Case reports of children with congenital deficiency of lacrimation do not indicate associated disturbances of autonomic function.[1-5] General disturbance of autonomic function is found in Penfield's description[6,7] of autonomic diencephalic epilepsy but is different from this syndrome in that it is episodic, does not occur in children, is associated with a definite organic lesion and is not marked by defective lacrimation. In some cases of postencephalitic parkinsonism, episodes of sham rage and sudden autonomic discharge have been reported[8-10] which though similar do not seem to belong to this group. The episodic phenomena described by Page[11] in young women with essential hypertension resemble closely the reactions of the children in this group, with the exception that excessive lacrimation rather than diminished tearing was the rule. The concept of autonomic imbalance put forward by Eppinger and Hess[12] and later elaborated by Wenger[13] refers too strictly to the predominance of either sympathetic or parasympathetic activity to encompass this syndrome.

One case reported by Engel and Aring[14] of a child who had severe bouts of vomiting associated with high fever had many points of similarity to those we report. The reactions in this case were more of the sham rage type but the excessive swings in blood pressure, drooling and deficient lacrimation were all present. At autopsy a small cystic lesion was found in the thalamus of this patient.

CASE REPORTS

Case 1. M. L. This patient was seen first at the age of 6 yrs., 5 mos., because of attacks of vomiting since the age of 6 mos. During the 29 months following her first visit, or until the age of 8 yrs., 10 mos., she was admitted to the Babies Hospital four times for treatment and study and between hospital visits she was seen regularly in the outpatient department. She was not seen again until recently at the age of 16 years.

Her parents were Russian-born and of Jewish extraction. They are both living and well. There

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are two normal siblings. There was one miscarriage at about 5 months and one sibling died of pneumonia at the age of 2 years. This child is said to have had cold hands and to have always been "ailing and drooling."

The patient was born at full term, normal delivery, birth weight 3.4 kg. Neonatal course was normal. Physical and mental development has always been slow. Menarche occurred at 14 years and menstruation has been normal.

At 6 mos. of age she began to have attacks of vomiting. These started usually after breakfast but occasionally after lunch or supper. She would vomit steadily for from 3 to 4 hours and then recover completely, eating the remaining meals with apparent relish. Attacks occurred every day for as long as three weeks at a time. She would then be free of attacks for a period of weeks or months. As she grew older the attacks seemed to be precipitated most often by emotional upsets. These attacks gradually disappeared after the age of 10 years.

Between the age of 6 to 12 months the hands and forearms gradually became blue and cold. Subsequently the feet were involved to a lesser degree. This condition has persisted to date and has remained a distressing complaint. During the first few years relief was obtained when the patient went to sleep.

Until about the age of 10 years the patient perspired so profusely when she went to bed that her bedclothes had to be changed about 1½ hours after retiring. She would also perspire and drool when excited and alarmed. This condition has persisted. During periods of emotional strain large irregular erythematous blotches appear consistently over the trunk, upper arms and back, extending up to the back of the neck. When last seen the patient stated that she had never cried with tears.

The patient has always been an unhappy, dejected-looking child with whom it was difficult to make contacts. She was easily upset emotionally and had frequent temper outbursts. She was withdrawn from associations with other children and got few satisfactions from school life.

Positive physical findings have remained much the same. She has always been a little underweight. The skin of the hands and forearms is cold, damp and blue. It is tight and rather inelastic and at the present time there are early but definite flexion contractures of the fingers. The skin of the feet is similarly involved but to a lesser extent. The conjunctivae and corneae appear normal. The deep reflexes are obtained only with reinforcement. Neurologic examination is otherwise negative. The blood pressure has varied from a low of 70/60 mm. Hg when the patient is asleep to a high of 180/170 mm. Hg when she is alarmed. It has always been extremely labile and the pulse pressure has usually been small. The heart is not enlarged. There is a grade II systolic murmur heard over the precordium. The femoral artery pulsations are present. Palpation of the abdomen reveals no abnormal findings.

The child has always been retarded in her mental development and made poor progress in her school work. Psychometric tests were given at 6 yrs., 5 mos. She scored 4 yrs., 6 mos., on the Stanford-Binet, intelligence quotient 70, and on the Goodenough scale she measured 6 yrs., 3 mos. The examining psychologist noted an outstanding difficulty in prolonged voluntary attention. A Rorschach test was not done.

Routine laboratory studies showed normal blood findings; urine was usually normal but occasionally showed faint traces of albumin. The results of capillary microscopy and skin temperature studies have been reported elsewhere.[35] A gastrointestinal series at one time showed complete pyloric obstruction at three hours. A subsequent examination was normal. An electroencephalogram done at 7 years was reported as grossly abnormal showing poorly defined alpha waves and a random mixture of big slow and fast waves. It was considered compatible with a diagnosis of convulsive disorder. No repeat tracings have been done. An intravenous pyelogram revealed normal renal outlines.

The following drugs have been administered without appreciable change in symptomatology: atropine, 3-diethylamino-2, 2-dimethyl-1-propanol (syntropan), ergotamine tartrate (gynergen-Sandoz), phenobarbital, Ryzamin B (Burroughs-Wilcome), ephedrine, papaverine hydrochloride, nicotinic acid, benzedrine and vitamin B (Viben-Viben).

Her present status at the age of 16 years is about the same. Her intellectual progress continues to be slow; she is in the eighth grade but not doing well. She still tends to drool and have high blood pressure when excited, and vomits easily under tension.

Case 2. R. K. This boy, of Jewish parentage, was first admitted to Babies Hospital at the age of 5 yrs., 6 mos., for intractable vomiting of 24 hours' duration. The father had had "vertiginous

attacks" following otitis in youth and also had frequent headaches. There was a family history of hay fever and asthma. There was one normal sibling 11½ yrs. of age. The mother displayed severe neurotic symptoms of life-long duration which were also reflected in a disturbed parent-child relationship.

The patient was born after a normal pregnancy and labor, weighed 2.4 kg. at birth, and had a normal neonatal period. At 3 mos. he had a respiratory disease, diagnosed as pertussis, during which there were no convulsions. Following this he seemed slowed in development, and had some vague visual disturbance. He sat at 12 mos., walked at 20 mos., but is said to have begun to talk at 16 mos.

He had previously been admitted six times to another hospital: three times for pneumonia, once for neurogenic vesical dysfunction manifested by urinary frequency and hypertonic bladder as demonstrated by cystometrogram, once for otitis media, and once for cyclic vomiting. A diagnosis of low lumbar spina bifida had been made and a brace recommended but never worn. In these early diagnostic surveys extreme mottling of the skin and failure to produce tears when crying had been noted.

At this admission physical examination was remarkable only for the obvious dehydration resulting from the vomiting and for the fact that his hands and face were chapped.

Until the time of his death in 1945 he was admitted to Babies Hospital a total of 20 times and several times elsewhere. All admissions were for intractable vomiting requiring the administration of parenteral fluids. Between these severe attacks, which occurred at intervals ranging from two weeks to six months, he vomited not infrequently in the morning.

During the course of his long acquaintance with this hospital the following facts emerged. His general muscular coordination was poor but there were no pathologic neurologic findings except that deep tendon reflexes were hypoactive. The blood pressure was extremely labile, ranging from 70/40 mm.Hg to 174/148 mm.Hg, the latter figures being obtainable under emotional stress. The vomiting seemed definitely related to psychic phenomena; for instance, on several occasions during vomiting episodes he was kept in a room by himself, but when told that he could go out on the ward with the other children as soon as his vomiting stopped he promptly recovered. He was moderately hyperactive on the ward, and given to rapid and unpredictable changes in mood. When emotionally upset, which was often, his motor overactivity became more marked and impulsive destructive behaviour would emerge. He seemed to try to be friendly and pleasant and was frequently disturbed at being rejected by the other children. Speech was somewhat indistinct.

The hemoglobin and red blood cell concentrations were consistently in the normal range. The urine never showed any formed elements, but occasionally contained faint traces of albumin during periods of dehydration. The blood nonprotein nitrogen level on two occasions during his early admissions was approximately 45 mg./100 cc.

Other special procedures included an electroencephalogram which showed absent alpha waves and high voltage slow waves but no focal signs. Cold pressor tests showed a surprising lack of pressor response, but apprehension would elevate the blood pressure markedly. A pneumoencephalogram was interpreted as being essentially normal but there was slight dilatation of the left lateral ventricle. He was given psychometric examinations on five occasions; his intelligence quotient was always about 85. Poor eye-hand coordination was noted in all tests with inadequate control of voluntary attention. Tests involving perception of form and spatial relationships were below his general level of achievement. The Rorschach test on two occasions, at 6 yrs., 5 mos., and 8 yrs., 10 mos., was interpreted as showing some constriction of interests and activities and a retreat from external stimuli. Some impulsive and explosive tendencies were noted.

On the ward it was found that under emotional tension he tended to manifest large erythematous sharply circumscribed blotches on the skin of the chest. These seemed to recur in the same places. At such times he would perspire profusely and begin to drool. The lack of tear production previously noted was confirmed. All these phenomena were so striking that he was thought to have, in addition to cyclic vomiting, autonomic imbalance possibly secondary to encephalitis due to pertussis.

Unsuccessful attempts at therapy included phenobarbital, diphenylhydantoin sodium (dilantin) and atropine. It was felt that the emotionally tense atmosphere of the home contributed to the recurrent vomiting episodes as a "trigger mechanism." Attempts to change the parental attitudes, including psychiatric care for the mother, were unavailing.

Finally he went to another hospital where exploration of the adrenal regions in search of a pheochromocytoma was carried out, but nothing abnormal was found. Sympathectomy was performed

also and, following this, the blood pressure was not quite so high but the vomiting attacks continued.

Because of the chronicity of his disorder and lack of response to all forms of treatment he was admitted to the children's ward of a psychiatric hospital in the hope that he could be stabilized away from the home environment. He remained there just one month, vomiting only on weekend visits home. While at home on leave from that institution he suddenly began to vomit blood, lapsed into coma and died at the age of 11 years. The medical examiner was content to assign the death to "acute cardiac dilatation" and there was no autopsy.

Case 3. L. K. This 8 yr. old boy of Jewish parentage has been studied in hospitals five times: once at the Neurological Institute of N.Y., twice at Babies Hospital and twice elsewhere. There is nothing relevant in the family history. His birth was normal but on the tenth day of life he was reported by nurses to have had convulsions. He did poorly during infancy, his motor development being definitely retarded. He did not hold his head till 8 mos., sat alone at 18 mos., and walked at 21 mos. He talked, however, at 2 yrs. His health other than the items which relate to the present discussion has been fair, but he has had moderately frequent respiratory disease.

At 8 mos. he was studied at another hospital because of slow development, peculiar skin blotching, poor weight gain and a habit of rubbing his hands and feet together. The sleeping blood pressure was 115/70 mm.Hg. A diagnosis of acrodynia was made.

Following this he improved somewhat, but at about 18 mos. began to have episodes of rigidity. He was accordingly admitted to the Neurological Institute where numerous laboratory tests gave normal results. Skin blotching persisted, and extreme sweating and drooling were noted. He was still considered to have acrodynia.

The episodes of rigidity, which have been interpreted retrospectively as tonic seizures, persisted and at present occur at rare intervals. He was admitted for study to Babies Hospital at the age of 4 yrs. On this occasion it was first discovered that he had an extremely variable blood pressure, ranging from 170/100 mm.Hg to 100/40. mm.Hg. The other features already mentioned were still present. Efforts to rule out the possibility of pheochromocytoma included abdominal massage which failed to produce hypertension, a normal intravenous pyelogram and perirenal air insufflation. The latter showed no tumor masses. Laboratory tests showed some anemia with a red blood cell count of about 3.5 million and hemoglobin of 9.5 gm./100 cc. blood. Urine occasionally showed a faint trace of albumin but no formed elements. An electroencephalogram showed high voltage, slow activity and absence of alpha waves. This was interpreted as being consistent with, but at this age, not diagnostic of, a convulsive state. Psychologic studies were done at 4 yrs., 3 mos.; he scored at age on both his Stanford-Binet and Merrill-Palmer scales. The Rorschach test responses were not regarded as unusual for his age. He was discharged with a diagnosis of autonomic imbalance.

Since then the main new development has been the appearance of attacks of severe vomiting lasting two or three days and requiring parenteral fluids. These usually start at about four o'clock in the morning and are associated with semi-stupor. Fever is, as a rule, absent at the beginning but appears before the attack is over.

He was studied a year ago at the age of 7 yrs. at another hospital where the major effort was to rule out pheochromocytoma. Histamine produced a fall in blood pressure and adrenalin gave equivocal results. Studies of his blood pressure in relation to his blood sugar level showed no correlation. Electroencephalogram showed a tracing similar to that already reported. Postural hypotension was observed. The final opinion was that he had a generalized disturbance of his central nervous system.

His most recent hospitalization was at Babies Hospital during one of his severe vomiting attacks. While in the stuporous phase his blood pressure continued high (160/110 mm.Hg), but as he improved his blood pressure fell. The relation of the hypertension to excitement was amply demonstrated in the course of a cold pressor test. He was accustomed to this procedure and evinced no fear at the thought of it. His blood pressure showed no change when his foot was immersed in ice water and, surprisingly, he complained of no pain; but subsequently when venipuncture was threatened the arterial pressure rose very promptly from an average of about 120/80 mm.Hg to 160/132 mm.Hg and as promptly fell when the fear was dispelled. At this time his parents complained that he had generally poor muscular coordination. However, his intellectual development was satisfactory and he was doing well in the second grade at school. On further questioning it was discovered that he had never cried with tears although he had never had any trouble with his eyes. Electroencephalogram

showed some suggestive spike and wave complexes. A pneumoencephalogram showed no abnormalities.

Under the assumption that this might represent a form of diencephalic epilepsy he was given anticonvulsant therapy including trimethadione tridione and phenantoin mesantoin. Since that time he has had no vomiting episodes of severity and the mother thinks that his general hyperreactivity is not so marked but it is obviously too early to ascribe the improvement to the medication.

Case 4. H. R. The patient, a boy of Jewish parentage, was first admitted to the Institute of Ophthalmology at the age of 18 mos. because of a corneal ulcer of the left eye. His father had been rejected by the draft board because of high blood pressure and a heart murmur.

The patient was born after a full term normal delivery and weighed 3.1 kg. at birth. The neonatal period was normal but he was always considered a feeding problem, never taking more than 50 cc. of formula at a time. At about 6 mos. of age his left eye was noted to be red and was treated by a physician. Because of failure of therapy he was admitted to the hospital. Here chemotherapy proved ineffective and finally perforation of the anterior chamber of the left eye occurred requiring covering by a conjunctival flap. Between this time and 3 yrs. of age, he was admitted five times for treatment of the left eye and for ulceration of the right cornea which appeared at 2 yrs. of age. Later it was noted that he had apparently absent lacrimation. To protect the vision in the right eye, lid adhesions were created and with this treatment the right cornea healed so that the adhesions could be released six months later. Because of recurrence of the lesion, however, new adhesions were created which have been left in place to the present. Meanwhile cicatrization of the left cornea is nearly complete so that the eye is sightless, and from the right his vision is impeded by slight scarring and by the smallness of the aperture left by the lid adhesions.

In addition to the ophthalmic difficulties it was noted that the patient was unusually reactive to relatively mild emotional stimuli as evidenced by extreme sweating, blotching of the skin of the chest, drooling and cold hands and feet. When the blood pressure was taken at such time, it was found frequently to be as high as 180/140 mm.Hg. Also he had an unusually great number of severe respiratory infections always associated with high fever. With these episodes he frequently vomited a good deal. At the age of 4 yrs. he had two convulsions associated with a febrile episode, with normal spinal fluid findings. Because of the repeated respiratory difficulty he was admitted four times to Babies Hospital. During these times he frequently showed bronchopneumonia by roentgenogram. On one occasion a bronchogram was done which was normal. Also he had his tonsils and adenoids removed without diminution in the frequency of pulmonary infection.

While on the ward a good opportunity was available for observing his reactions. Because of his hyperreactivity he was somewhat difficult to handle, but appeared to do better in the impersonal atmosphere of ward life than at home; in particular, he ate better and gained weight. His blood pressure has been found as low as 80/40 mm.Hg when standing, more frequently around 120/80 mm.Hg when relaxed in bed, and frequently as high as 175/130 mm.Hg when excited.

In the laboratory his urine was found always to be free of albumin or formed elements. His blood has consistently showed an anemia with hemoglobin of 9-10 gm./100 cc. and red cell count of 3.5-4.0 million/cmm.

Several special procedures have been done. Before he had become acclimated to a cold pressor test, the excitement it produced caused a tremendous rise in blood pressure before exposure to cold, but with careful conditioning it was found that there was no pressor response, and surprisingly there was very little pain associated with immersing his foot in ice water. When under a state of tension so that his blood pressure was maintained at about 150/130 mm. Hg, benzodioxane (an adrenolytic substance[16]) was given intravenously. There was a prompt fall of blood pressure, but within five minutes a rise was readily induced by emotional stimulation.

Psychometric rating was not completely satisfactory; he obtained an intelligence quotient of 80 but this was thought to be an inadequate estimate because of his poor cooperation and visual handicap. In his general behaviour on the ward he seemed to be equal to his contemporaries. An electroencephalogram was reported as being normal. A pneumoencephalogram showed suggestive mild brain atrophy. Also, the course of the aqueduct of Sylvius showed an anterior convexity as it left the third ventricle instead of the usual posterior one. That this may have been an artifact cannot be excluded as stereoscopic studies were not made.

This patient has subsequently undergone a neurosurgical procedure. The reasons for doing this and the early results will be reported in a companion article.[17]

Case 5. S. G. A white Jewish girl, 6 yrs. of age, was seen at The New York Hospital and died 4 years later. Her chief trouble was a series of vomiting episodes, often accompanied by unexplained fever, severe enough to necessitate hospital admission on 14 occasions. In addition she had enuresis nearly every night of her life, excessive sweating, transitory blotching of the skin, mumbling speech and, according to the parents, obesity. Her mother suffered from migraine headaches. One previous child had died at 8 mos. of age. The birth of the patient was noteworthy because the nurse held back the baby's head pending arrival of the obstetrician. Resuscitation was needed and there were numerous spells of cyanosis in the newborn period; furthermore, she did not suck well. Several transfusions were given.

She was a pleasant, cooperative, plump girl, who weighed 21.2 kg. when first seen at 6 yrs. of age and who was 108 cm. tall. Her blood pressure was 200/170 mm.Hg, pulse 120/min. and respirations 22/min. When slightly excited she overreacted with perspiration, dilation of pupils and blotching of the skin. The red skin areas were sharply demarcated during these periods of excitement. They were bilaterally symmetrical over the shoulders and hips, but in the case of the forehead the red right half was separated from the paler left by the midline. The vessels of the ocular fundi were normal except for dubious arterial constriction. Pulsations of the radial, femoral and dorsalis pedis arteries were faint and the hands and feet were cold, red and damp. Deep tendon reflexes were absent.

On the first hospital admission, the red blood cells numbered 4.8 million and the white cells 6 thousand/cmm. The hemoglobin was 13.9 gm./100 cc. Serum electrolytes in mg./100 cc. were as follows: calcium, 10; phosphorus, 5; chlorine as sodium chloride, 660; urea nitrogen 11.0. Choline esterase activity of blood was normal, and blood phosphatase 7.7 Bodansky units. A year later, a sodium level was 140 mEq/l, and other values were unchanged. Mantoux and Kline tests were negative. A glucose tolerance curve showed a rise in 80 minutes from 95 to 204 mg./100 cc. blood after ingestion of 40 gm. of glucose, with a return to 108 after 120 minutes. In the course of the 14 admissions 65 urinalyses showed specific gravities varying from 1.010 to 1.031. Albumin was found only once, a few days before death, but a trace of reducing substance was noted nine times. No pus or blood was ever seen and granular casts only once, just before death.

Retrograde and intravenous pyelograms were normal, as was a pneumoencephalogram and a gastrointestinal X-ray series. The electroencephalogram was characterized by frontal records with high voltage, many 16 per second waves, and some 7 and 3 per second waves. The left parietal record showed many fast waves which were absent on the right; a similar result was obtained with occipital leads. Her intelligence quotient was 86, with the comment that her speech was retarded more than other accomplishments.

With rest in bed her blood pressure fell to 110/70 mm.Hg. The sight of a hypodermic needle, an injection of adrenalin or of water, placing one foot in ice water or any other cause of excitement served equally well to raise the blood pressure to the admission level, with a return to normal over a two or three hour period. Sweating and blotching of the skin ceased as soon as the stimulus was withdrawn. Massage of the abdomen had no especial effect. Methacholine chloride (mecholyl) subcutaneously caused a temporary fall in arterial pressure of 20 mm.Hg when given during a period of hypertension.

Two operations were performed in search of a pheochromocytoma. None was found. After each operation her course was stormy with high fever, pneumonia, and ulceration first of the left cornea and then the right. These ulcerations were thought to be due to ether burns or to the fact, then noted for the first time, that lacrimation was highly deficient.

The final admission was because of severe headache, vomiting and fever. Four days before death she had a trace of albumin in the urine and a blood urea nitrogen of 262 mg./100 cc. Later, casts were seen. She lapsed into coma and died at 10 yrs. of age.

No pheochromocytoma was found at autopsy despite a thorough search which included sectioning several lymph nodes in an attempt to demonstrate ectopic adrenal tissue. The brain was likewise essentially normal both grossly and microscopically; in particular, no abnormalities were noted in the basal ganglia and floor of the third ventricle. The kidneys were large, weighing 150 gm. each. After stripping the capsule, the surface was seen to be covered with many elongated red dots. The cortex was pale, the pyramids red, and there were hemorrhages in the pelvis. Microscopically, the glomerular tufts were seen to be structurally normal and there were no epithelial crescents. Bowman's space was filled with a protein precipitate and in a few glomeruli there was an occasional red cell. Occasionally,

near the origin of a tubule a mass of swollen epithelial cells was seen; in places this had degenerated into a homogeneous pink agglomerate. The epithelial cells of the convoluted tubules were swollen and vacuolated and some lacked a nucleus. The lumina of the tubules contained precipitated protein. The epithelium of some of the collecting tubules was irregular. The small arteries had normal walls. In the liver there was some vacuolation of cells in the peripheral zones. The heart was slightly enlarged.

Comment

The foregoing cases appear to represent examples of a single syndrome. The points of resemblance are brought out in the accompanying correlation table (Table I). The outstanding features are defective lacrimation and response to anxiety with sweating, skin blotching and hypertension. These features were found in all five cases. Drooling

TABLE I
Correlation of Findings in the Cases Reported

	M.L.	R.K.	L.K.	H.R.	S.G.
Defective Lacrimation	++	++	++	±±±±*	+++*
Reaction to Anxiety					
Hypertension	++++	+++	±±±±	++++	++++
Skin Blotching	++++	++	±±±	++++	++++
Sweating	++++	++++	±±±±	++++	++++
Drooling	++	+++	++	++++	?
Cold Hands	±±±±°	?	±±±	+++	+
Hyporeflexia Motor Incoordination	+++	+++	+++	++	++
Frank Convulsive Phenomena	0	0	++	+	0
Mental Retardation	+++	++	0	+	++
History of Possible CNS Injury	0	+	0	0	++
Cyclic Vomiting	++++	±±±±	++	0	++++
Frequent Pulmonary Infection	0	+++	0	++++	+++
Abnormal EECG	+++	+++	+++	0	+++

* Had corneal ulceration.
° Persistent, even when not under tension.
± Chief complaint.

occurred as a major feature in three, and four showed changes in peripheral circulation as evidenced by cold hands with emotional tension. In one case the latter finding was constant and not limited to periods of stress, the presenting complaint being acrocyanosis. The results of studies of skin temperatures of this patient were previously reported[15] with the interpretation that the malady was of central origin.

Some degree of mental retardation was a feature in three of the children. M.L. had an intelligence quotient of 70. R.K. and S.G. were in the dull group with intelligence quotients of about 85. L.K. had a much retarded early developmental history, but recently a psychometric examination has shown him to be of about average intellect. Since, however, he is the child of highly intelligent parents, this is somewhat below expectancy. H.R. also has had a delayed developmental history, and at present has an intelligence quotient of about 80. This rating, however, is thought to be an inadequate estimate of his capacities because of difficulties in testing and his visual disturbance. One wonders if, like L.K., he may not come up to average in the future. It is of interest

that in two of the patients, M.L. and R.K., the pattern of psychologic test responses is that often associated with diffuse organic involvement of the central nervous system.

Two of the children, M.L. and R.K., were seen in the psychiatric clinic. It was thought that the behavior and personality disturbances were precipitated by emotional stimuli and a disturbed home atmosphere but that the basic disturbance was in the nature of a diffuse encephalopathy. The Rorschach test responses of R.K. were compatible with this impression. It is of interest that the Rorschach test of L.K. was not thought to be abnormal. It is considered that attention to the emotional environment of these children may alleviate but will not cure their symptoms.

Cyclic vomiting was a conspicuous feature in four of the five cases. In the fifth, the patient is still younger than the age of onset of the vomiting in some of the others. He has already shown a tendency to vomit more readily than other children. It is the impression of those who have seen the vomiting episodes in these children that nausea was not a feature. Since vomiting is so outstanding in this group the records of all cases with the diagnosis of cyclic vomiting in the files at Babies Hospital were examined. No additional cases were found which could definitely be considered to exhibit this syndrome. One reason may be that the records lack repeated blood pressure readings and comment with regard to lacrimation.

Whether the syndrome represents a congenital or an acquired defect in the central nervous system is not clear. In two cases it is at least possible that postnatal influences may have played a causal role. R.K. had a questionable history of pertussis at three months; the parents date all his difficulties from this time. S.G. had a traumatic birth with a stormy neonatal course. The question of racial influence is raised by the fact that all of our cases are of Jewish parentage, but the small size of the group makes this of doubtful significance.

The hyporeflexia, poor motor coordination and mental retardation were the only neurologic findings which did not seem related to the autonomic nervous system. Their significance is not clear but perhaps they add to the evidence for a central origin of the difficulties.

The fact that three of the patients had frequent pulmonary infections might indicate aspiration of the excessive saliva or the presence of overabundant bronchial secretions.

The stated complaint was different in each of the five cases. Coldness and blueness of the hands was the reason why M.L. was originally brought to the hospital, although subsequently her cyclic vomiting undoubtedly caused most of her difficulty. R.K.'s chief complaint from the beginning was vomiting. L.K.'s emotional hyperreactivity and peculiar skin manifestations were the main causes of concern to his parents. H.R.'s presenting problem was the frequency of corneal ulceration, which had nearly blinded him. The other features became apparent only with further study. S.G.'s parents sought medical advice because of her poor enunciation and somewhat short stature, but subsequent admissions to the hospital were for vomiting.

The possibility that undetected underlying disease of familial type was responsible for the symptoms has been considered. Renal disease seems unlikely as the primary factor since urinalyses have in general been normal in these patients and since elevations of blood pressure have been so transient; also there have been no chemical findings of nitrogen retention except terminally in the case of S.G. In view of this lack of reason to implicate the kidneys it is interesting that S.G. apparently died in uremia. Renal involvement in this instance may have been secondary to the hypertension.

The possibility of pheochromocytoma has caused considerable concern. In two cases, R.K. and S.G., surgical exploration of the adrenal region was carried out and no tumor found. A subsequent autopsy of S.G., where a more widespread search was made, failed to reveal any neoplastic lesion. L.K.'s adrenals were visualized by perirenal air insufflation to no avail. This patient has also been subjected to the administration of intravenous histamine with a consequent fall of blood pressure rather than the expected rise. H.R. was tested with intravenous benzodioxane[16] which is adrenolytic. Under the emotional tension of the test his blood pressure remained high until the drug was introduced when it fell about 150/120 mm. Hg. to 120/90 mm. Hg. When emotionally stimulated, however, within five minutes of the injection, when the drug should still have been active, the pressure promptly rose to its former level. This may indicate that when the patient is under tension the blood pressure is only partially maintained by circulating epinephrine, and can also be influenced by neurogenic control. Also against pheochromocytoma are the cholinergic responses shown by these patients, i.e., sweating, salivation, and skin blotching.

Throughout the above discussion it has been assumed that the syndrome is the result of central nervous system disorder. The reasons for such an assumption follow: 1. The most striking features are those of diffuse involvement affecting both cholinergic and adrenergic systems. 2. The roentgenographic evidence of disturbed gastric function in M.L. demonstrates the involvement of more than one anatomic system. 3. The findings of hyporeflexia, motor incoordination, mental retardation and abnormal electroencephalographic records point to diffuse disturbance in the brain.

Attempts to localize the site of origin of these symptoms and signs in the light of the data available are at best purely speculative. Cushing,[18] on the basis of experiments with injection of pituitrin and other substances into the lateral ventricles of the brain as well as a review of the literature, postulated the existence of a parasympathetic center in the diencephalon. In his experiments with pituitrin injection his patients showed many features exhibited by this group. Some of Penfield's cases[6,7] with tumors of the third ventricle or trauma involving that region showed similar symptoms. Engel and Aring's case[14] with a demonstrated lesion of the thalamus, as already discussed, had very similar features. It is unfortunate that autopsy findings are available in only one of the patients of this group. In that case no central nervous system lesion was found. Perhaps the syndrome represents a functional disturbance not accompanied by alteration of structure. It has seemed most nearly justified to incriminate the diencephalon. A decisive localization awaits more evidence. The early results of a neurosurgical procedure performed on H.R. are reported in an accompanying paper[17] and may have some bearing on this question.

Recently two more children, siblings, who resemble those reported, have been called to our attention. Though incompletely studied as yet they are known to have transitory hypertension, skin blotching and a history of crying without tears. One may wonder whether this syndrome, possibly incomplete, is not rather common.

Summary

Five cases have been reported with symptoms and findings so similar as to constitute a clinical entity. The common features in this group are: 1. a deficiency of lacrimation; 2. an abnormal reaction to mild anxiety characterized by transient extreme elevation of blood pressure, excessive sweating, salivation to the point of drooling,

and the development of sharply demarcated erythematous blotches on the skin, biliterally symmetric, and tending to recur in the same or similar configurations. The findings seem best interpreted as a central, possibly congenital, disturbance of autonomic function. An origin in the diencephalon has been suggested. The most difficult feature to interpret from a neurophysiologic point of view is diminished rather than excessive lacrimation.

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Addendum

Since this report was submitted for publication, one of the cases mentioned above has been more closely observed and a new case has been found. Both of these exhibit all of the major features described, bringing the total of carefully studied typical cases to seven. An eighth case has been seen which fails to show blood pressure and emotional instability, but does show defective lacrimation (with a corneal ulcer), drooling, vasomotor changes in the hands, hyporeflexia and motor incoordination.

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SPANISH ABSTRACT

Disfunción Automática Central Con Lacrimación Defectuosa. I. Informe de Cinco Casos.

Se han reportado cinco casos con síntomas y descubrimientos tan similares como para constituir una entidad clínica. Las características comunes en este grupo son: (1) una deficiencia de lacrimación; (2) Una reacción anormal a ansiedad moderada caracterizada por la extrema elevación pasajera de la presión arterial, exudación excesiva, salivación hasta el punto de babear, y el desarrollo de manchas eritematosas agudamente demarcadas en la piel, bilateralmente simétricas y con tendencia a repetirse en las mismas o similares configuraciones. Los descubrimientos parecen interpretarse mejor como desorden de función automática, posiblemente congénita. Se ha sugerido un origen en el diencéfalo. La característica más difícil a interpretar de un punto de vista neurofisiológico es la lacrimación disminuida más bien que excesiva.

630 West 168th St.

CENTRAL AUTONOMIC DYSFUNCTION WITH DEFECTIVE LACRIMATION

II. Preliminary Report of Effect of Neurosurgery in One Case

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IN A COMPANION article[1] five cases have been reported which appear to constitute a new syndrome. This seems to represent a central disturbance of autonomic function characterized primarily by abnormal reaction to mild excitement with transient arterial hypertension, diaphoresis, development of red blotches on the skin, excessive salivation and persistently deficient lacrimation. In this report a presentation of the early effects of an operation in which the tentorium was split will be given. It is hoped that this may help to throw some light on the nature of the central disturbance.

CASE REPORT

The case of H.R. has already been summarized in the preceding article.[1] Briefly, he is a 4 yr., 10 mos. old boy whose presenting difficulty was intractable corneal ulceration leading to complete opacification of the left cornea and moderate scarring on the right. To protect the vision in this eye, lid adhesions had been created, thus markedly reducing his field of vision. The ulcerations were found to be the result of complete absence of tears. In addition to this he was found to have extremely labile blood pressure, to drool almost constantly and to develop excessive diaphoresis and skin blotching under emotional tension. Skull roentgenograms revealed cranio-facial disproportion, the calvarium being large but markedly dolichocephalic. Pneumoencephalogram had shown what was interpreted to be an anterior bowing of the aqueduct of Sylvius where normally the curve is slightly convex in a posterior direction. This suggested that there might be some pressure dorsal to the aqueduct altering its normal course. Since there were no stereoscopic views it cannot be stated with certainty that this was not an artifact resulting from an overlying shadow.

One of us (T.B.) had previously had occasion to perform a tentorium splitting operation for unrelated reasons in a 7 month old baby. One of the unexpected results reported by the parents in this case was that the baby, who prior to operation had never cried with tears, subsequently began to lacrimate obviously when crying. With this experience in mind the pneumoencephalogram of H.R. was reviewed with regard to the apparent aqueductal distortion. It was felt that this might represent pressure due to partly trapped cerebrospinal fluid which could be relieved by splitting the tentorium; or it might be due to congenital malformation of the tentorium and base of the skull resulting in constriction or displacement of the developing midbrain. After much deliberation it was decided that the gravity of the patient's condition warranted an attempt to relieve the situation surgically.

Accordingly under pentothal-ether anaesthesia a right occipital bone flap was reflected. The occipital lobe was elevated with gentle retraction, exposing the right half of the tentorium. The first abnormal finding consisted of fairly large venous channels lying in the substance of the tentorium 4 to 5 mm. central to the right lateral sinus. Emptying into this from the brain substance were several prominent veins which had to be divided in the process of elevating the occipital lobe. When the incisura of the tentorium was exposed a bulging cuff of arachnoid could be seen surrounding the midbrain.

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The arachnoid itself was thickened and presented a dense mesh of trabeculae. When this cuff was incised cerebrospinal fluid spurted forth under considerable pressure although there was no evidence of generalized elevation of intracranial pressure. A radial incision was now made in the tentorium from the incisura to the accessory venous sinus described above, and another incision was then made at right angles to the first extending in a posterior direction. As these incisions were made the edges of the tentorium gaped as if the structure had been under considerable tension. Following this the dura, skull and scalp were closed in routine fashion. The total duration of anaesthesia was about four hours. The postoperative course was satisfactory from a neurosurgical point of view although the patient's temperature reached a peak of 39.4°C. during the first two or three days. Thereafter he had decreasing daily temperature elevations for 10 days, after which he had no more fever. He had a moderate subgaleal collection of cerebrospinal fluid which was spontaneously reabsorbed after two weeks.

His general behaviour postoperatively was of considerable interest. Within a day or two the nurses began to comment that his salivation was remarkably diminished. Also blood pressure readings taken at frequent intervals revealed that even when under emotional stress during the first three days it did not rise over 110/74 mm.Hg. A third feature was the fact that skin blotches so often noted preoperatively now failed to appear. These changes toward normal persisted for about two weeks after operation when some regression was noticed. His salivation increased and the other phenomena gradually returned, so that three weeks postoperatively he again exhibited all the cutaneous, salivary and hypertensive phenomena as previously.

With regard to lacrimation, however, the course was more favorable. At first no changes in his eyes were noted, but six days after operation actual tears were observed to flow from the left eye; from that time on his eyes have remained continuously moist. Prior to the procedure he required drops of Ringer's solution in both eyes every two hours to maintain any moisture, but since then he has had no drops at all and his corneae have remained in good condition. The conjunctivae have acquired a healthy appearance and are no longer injected. Before operation he usually awoke with stringy exudate at the lid margins, but this has now almost disappeared. When crying, while he does not produce tears as do other children, some moisture wells up in both eyes, more than he usually has. Incidentally his nose now runs when he cries which did not happen before. It is felt that it will now be safe to remove the lid adhesions of the right eye and thus expand his field of vision. If the corneae then continue to remain healthy the possibility of corneal transplant will be considered; this had previously been out of the question.

At the present time, over three months after operation, the patient is in general good health. His mother reports, moreover, that his reaction to excitement is not so great as formerly, and that his skin blotching and drooling have diminished. His blood pressure in recent office visits when under some excitement has been about 136/110 mm.Hg.

Any attempt to interpret the significance of these changes seems premature at this time. One point must be considered; namely, whether anaesthesia alone could have produced the postoperative effects. In answer it can be pointed out that for several other procedures (lid surgery, bronchoscopy, and tonsillectomy) he has had frequent short periods of anaesthesia and for pneumoencephalogram ether anaesthesia for nearly two hours without any observable change in his general condition. It may be that the early transitory effects on his skin blotching and blood pressure were the result of the anaesthesia, but it is difficult to think that the change in lacrimation which became manifest more slowly and has persisted could be due to anaesthesia alone.

Summary

The postoperative changes in a 4 yr., 10 mos. old boy with central autonomic dysfunction associated with defective lacrimation are reported. The operative procedure was division of the tentorium on the right side. Immediately following operation there was a transitory disappearance of the lability of blood pressure and abnormal reactions to mild anxiety. These features returned to their preoperative state within three weeks, but since then appear to have abated somewhat. Lacrimation, however, first made its appearance about six days after the operative procedure and has persisted to the time of writing, over three months later. Exact interpretation of these phenomena has not been attempted.

Addendum

Since this report was submitted for publication the eyelid adhesions on this patient have been taken down. The tearing has continued to be greater than before operation, but despite this the ulcer was reactivated and after four weeks it was necessary to reclose the eye. It is thought that perhaps corneal anaesthesia has more importance with regard to ulceration than the defective tearing.

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Spanish Abstract

Disfunción Automática Central Con Lacrimación Defectuosa. II. Informe Preliminar del efecto de neurocirugía en un caso.

Se reportan los cambios después de la operación en un niño de cuatro años diez meses con disfunción automática central asociada con lacrimación defectuosa. El procedimiento operativo fué la división del tentorio en el lado derecho. Inmediatamente después de la operación hubo una desaparición de la labilidad de la presión arterial y las reacciones anormales a ansiedad moderada. Estas características volvieron a su estado de antes de la operación dentro de tres semanas, pero desde entonces parecen haber disminuído algo. La lacrimación, sin embargo, apareció por la primera vez seis días después del procedimiento operatorio y ha persistido hasta el tiempo cuando esto fué escrito, después de más de tres meses. No se ha tratado de dar la interpretación exacta a estos fenómenos.

630 West 168th St.

STUDIES IN THE RELATION OF THE HEMOLYTIC STREPTOCOCCUS TO RHEUMATIC FEVER

VI. Comparison of Streptococcal Antihyaluronidase with Antibodies to Other Streptococcal Antigens in the Serum of Patients with Rheumatic Fever and Acute Streptococcal Infection: Mucin Clot Prevention Test

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THE evidence suggesting some relation between Str. hemolyticus and rheumatic fever has not identified any particular constituent or property of this organism as a causative factor. In order to verify and elucidate the role of that organism in the etiology and pathogenesis of rheumatic fever, the relations of a great number of streptococcal constituents and products to the rheumatic process must be studied. One of these is hyaluronidase produced by Str. hemolyticus. The possible role of this enzyme in the pathogenesis of rheumatic fever has been the subject of some recent speculation[1] based on the facts that rheumatic fever is a disease of hyaline connective tissue, that hyaluronic acid, which characterizes hyalin, is digested, or depolymerized, by hyaluronidase,[2] and that Str. hemolyticus is one of the bacterial species which produces this enzyme.[3] Moreover, although it was formerly thought that few strains of Str. hemolyticus produced hyaluronidase,[4,5] recent evidence has indicated that in all probability every strain of this organism liberates minute amounts of this enzyme into the tissues of its host.[6,7]

The effect of the enzyme hyaluronidase can be exhibited in two ways: *in vivo* as a spreading factor, and *in vitro,* by its ability to reduce the native, highly polymerized hyaluronic acid into small molecules of this substance. In the former direction, a special susceptibility of tissues of the rheumatic host to this enzyme was suggested by Guerra,[8,9] who described an unusually high rate of spread of dye-hyaluronidase mixtures in the skin of rheumatic subjects. This observation has not, however, been confirmed in these laboratories.[10]

The ability of the enzyme to be measured *in vitro* by its digestion of hyaluronic acid has also been applied here to the problem of rheumatic fever. In this case serum antibodies to the enzyme have been measured, since the free enzyme cannot be found in the blood.

The measurement of neutralizing antibodies to hyaluronidase depends on a method of measuring the enzyme itself. In addition to the purely chemical methods which measure the products of degradation of hyaluronic acid, three other methods have been described: the turbidimetric test, the viscosimetric method, and the mucin clot prevention test. All

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of these are physicochemical methods which depend largely on the reduction in size of the hyaluronic acid molecule from its original form to the depolymerized state. Since they have been discussed in the recent review of hyaluronidase by Meyer,[1] these methods will be mentioned here only briefly.

The viscosimetric method, first described by Madinaveitia and Quibell,[11] depends on the fact that the viscosity of a solution of hyaluronic acid is reduced as its molecular size is decreased by the action of the enzyme. The measurement of hyaluronidase by this method involves incubation of the enzyme with a known amount of hyaluronic acid and repeated determinations of the viscosity of the mixture in order to estimate the time required for a standard reduction in viscosity. The turbidimetric method, described by Kass and Seastone,[12] makes use of the fact that, while hyaluronic acid exists at a low pH as a stable turbid suspension, the depolymerized form presents a clear solution. Again, the time required for a standard reduction in turbidity of a solution of hyaluronic acid in the presence of hyaluronidase is the measure of the enzyme added.

The mucin clot prevention (M.C.P.) method, which was first described by Robertson, Ropes and Bauer,[13] depends on the fact that, where native hyaluronic acid is precipitated by acid in the presence of protein into a typical white fibrous "mucin" clot,[14] the depolymerized hyaluronic acid is brought down under these conditions as a flocculent precipitate.

Of the three methods the M.C.P. test is best suited to multiple and serial studies of neutralizing antibodies and was therefore chosen for this study. The results of such measurements in patients with streptococcal and rheumatic infection will be presented in relation to similar work done here with other antigens.

The investigation in this laboratory of possible relations between Str. hemolyticus and rheumatic fever has been directed largely toward a search for any constituents or products of Str. hemolyticus toward which the tissues of the rheumatic patient might show an abnormal reaction. In the immunologic field Str. hemolyticus has been fractionated by physical means into three parts, and some evidence has been offered that these represent, respectively, the cell wall, the cytoplasm and the nuclear contents of the streptococcal cell.[15] Of these fractions two, the cytoplasmic particles, (CP), and the supernate or nuclear fraction, (S), have been used in extensive serologic tests, in correlation with antistreptolysin tests.[16] It has been found that in rheumatic fever and after streptococcal infections the antibody titers to these antigens are elevated, but that the extent of this elevation bears no relation to the clinical phases of rheumatic fever.

Studies in rheumatic fever involving streptococcal hyaluronidase have also been in progress in the course of this investigation. The failure to confirm unusual spreading effects of hyaluronidase in the skin of rheumatic subjects has been mentioned above.[10] In the serologic field, the titer of neutralizing antibodies to streptococcal hyaluronidase has been measured in normal subjects, patients with streptococcal disease and active and inactive rheumatic infection.[7] It has been found that the titers of this antibody vary among different age groups in the normal population in a manner similar to that in the case of antistreptolysin and of antibodies to the two streptococcal antigens mentioned in the previous paragraph. In convalescents from scarlet fever and streptococcal pharyngitis, the streptococcal antihyaluronidase titer was found to be elevated in comparison with titers existing at the onset of the disease. In active rheumatic carditis the titers were also elevated to a greater extent in the average than those following the streptococcal infections.

It is this last mentioned difference between the mean antihyaluronidase titer in active

rheumatic fever and that found after streptococcal infection which provided the impetus to the present study.

Methods and Materials

The technics of the serologic tests employed have been presented elsewhere[7, 16] and will not be repeated here. For the study of antibody response to these antigens in acute streptococcal disease, blood specimens were collected from children with scarlet fever at the Philadelphia Hospital for Contagious Diseases during the first half week and during the third week of the disease. In a number of these cases, an additional specimen was drawn four months later.

In the case of rheumatic patients the blood specimens were drawn at weekly, biweekly or monthly intervals, depending on the severity of the rheumatic process, in correlation with the clinical studies to be described below.

Blood specimens were collected with a minimum of sodium citrate as anticoagulant, in order to allow for the determination of the ESR, WBC count, and Hgb. The plasma was drawn off each blood specimen and frozen as soon as the tests had been completed. When a specimen was to be tested, it was thawed, cleared by centrifugation of the fibrinogen which had precipitated on freezing and heated at 56°C. for 30 min. to inactivate complement. A single dilution of 1:8 or 1:16 was made of each serum in sufficient amount to allow for the two complement fixation tests, including controls for the detection of anticomplementary activity of the sera, the antistreptolysin test and the anti-hyaluronidase test.

The rheumatic patients were studied in active, convalescent and quiescent stages of the disease. They were usually seen first in the wards of The Children's Hospital of Philadelphia or of the Philadelphia General Hospital. Many of them were studied in the wards of the Children's Seashore House at Atlantic City during the chronic, active and convalescent stages of the illness. They were then followed at the Rheumatic Fever Clinics of the first-named institutions in the quiescent stage. In some cases, of course, the entire cycle was repeated.

The patients were examined at least every two weeks while in the acutely ill or convalescent wards and at each visit to the Clinics. These examinations included the following: symptoms—anorexia, headache, precordial, abdominal, or arthritic pain, cough, dyspnea and epistaxis; physical signs—cardiac rate and rhythm, distance of apex beat from the mid-sternum, murmurs, with distance of transmission of each, and other adventitious sounds, palpable thrills and friction rubs, hepatic enlargement and edema, rashes, subcutaneous nodules and chorea. Laboratory examinations included the ESR, WBC count, and Hgb. The vital capacity was usually determined at biweekly intervals, and ECG were taken as required. The ESR was done by a method described elsewhere.[17] It involved a series of readings of the erythrocyte level at five minute intervals, in order to determine the rate of free fall of the corpuscles, and a correction for the relative volume of erythrocytes.

Only those patients in whom the diagnosis of active rheumatic fever was beyond doubt were selected for serologic study. All of these children had active rheumatic carditis, except for the cases of polyarthritis included in Table III.

The recording of clinical evidence of rheumatic activity in correlation with the serologic titers presented a problem. A considerable part of the clinical data was kept in graphic form in the records of this investigation. However, an attempt to present all such data in graphic form in this paper was abandoned because of the necessary complexity of such graphs. On the other hand, the manifestations of active rheumatic disease are so protean that no one or two clinical signs can measure the activity in all cases. The ESR is probably the most sensitive single indicator of activity of the rheumatic process, but it has been shown that this test may be unreliable in adolescent and overweight children,[17] in right-sided heart failure,[18, 19] and in patients receiving prolonged full dosage of salicylates.[20–22] Finally, there are some patients in every series of sufficient size whose ESR is within normal limits, although there is unquestionable clinical evidence of an active rheumatic process.

For the recording of the clinical evidence of the degree of rheumatic fever, therefore, it was decided to show the ESR, temperature, resting pulse rate, and such episodes as polyarthritis, carditis and cardiac failure. The criteria of quiescence of the rheumatic process included the fall to a plateau level of the ESR, of the size and rate of the heart, and of murmurs and their extent of transmission; a stable pulse rate, absence of significant symptoms and signs, and general well being.

None of the patients with rheumatic fever or streptococcal infection received massive salicylate therapy, sulfonamides or penicillin.

Results

Serum Titers of the Respective Antibodies in Rheumatic and Streptococcal Infection

It is known that antibody titers to streptococcal antigens are found to be elevated following both streptococcal and rheumatic infection. In the case of antistreptolysin titers a mass of such data has been presented during the last 15 years,[23] and similar results with the other three antibodies under discussion have been reported from these laboratories.[7,16] Since the publication of those reports, the amount of clinical material has been increased considerably in all three groups, the normal children and those with strepto-

TABLE I

Mean Titers of Antibodies to 4 Streptococcal Antigens in Streptococcal and Rheumatic Infections

	Antihyaluronidase		Antistreptolysin		Anti-CP		Anti-S	
	Titer	Log_2 Titer	Titer	Log_2 Titer	Titer	Log_2 Titer	Titer	Log_2 Titer
Streptococcal Infection (149 cases)	45	5.5	148	7.2	62	5.96	13	3.68
Active Rheumatic Fever (126 cases)	480	8.9	256	8.0	111	6.8	24	4.58
Difference in Log_2 Titer between Streptococcal and Rheumatic		3.4		0.8		0.84		0.9
Ratio of Rheumatic to Streptococcal	10.6		1.74		1.79		1.87	

coccal and rheumatic infections. These additional data have in all cases agreed essentially with earlier data in the respective categories. Minor differences, such as a slight widening of the range of titers of presumably normal children, have not altered the mean values in any of the groups. Accordingly, there will be no repetition here of comparative serologic data between normal children and the streptococcal-rheumatic group of patients.

Between these two groups of patients, however, a small but consistent difference was found in the case of the antistreptolysin, anti-CP and anti-S tests, the rheumatic group always showing a greater mean titer by somewhat less than a single twofold dilution. In the case of antihyaluronidase, however, a substantial difference was noted, the mean titer in active rheumatic fever being slightly more than 10 times that found in streptococcal infection. Table I shows these differences.

In Table I it is seen that the mean antihyaluronidase titer found in active rheumatic fever has a logarithm (to the base 2) 3.4 greater than that found in the streptococcal infections under investigation. This difference was in the case of the other three antigens considerably smaller and was uniform within a narrow range, between 0.8 and 0.9. This difference between the data by the antihyaluronidase test, on the one hand, and the other three tests, on the other, is highly significant. Among the other three tests, however,

statistical treatment indicates that there is no significance to the respective differences in logarithmic titer of 0.04, 0.06 and 0.1.

Because of this difference between the antihyaluronidase test and the others, the individual percentage-frequency-distributions of titers in the two groups were charted for each of the four tests. In these charts, shown in Fig. 1, the distribution of titers in both clinical groups is in each case represented by columns set side by side. Each column

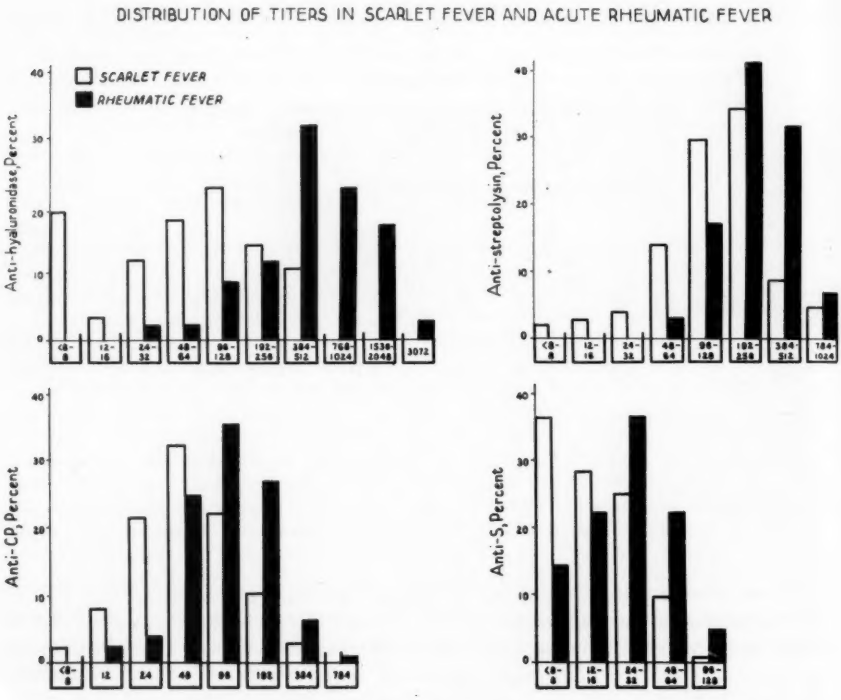


FIG. 1. Percentage-frequency-distributions of antistreptococcal antibody titers in active rheumatic fever and following streptococcal infections.

shows, for streptococcal and for rheumatic patients, the percentage of the total in that clinical group which was found in the range of titers indicated. It can be seen in Fig. 1 that the range of titers of patients with active rheumatic fever was somewhat higher than those of convalescents from streptococcal disease. On comparing the data between the two clinical groups, however, it is seen that in the case of antistreptolysin, anti-CP and anti-S, there is a fairly close relation between the titers found in the two diseases, the greatest frequency for each disease usually occurring at the same or neighboring titers; in the case of antihyaluronidase, however, the separation of titers for the two clinical groups is definitely of a greater order.

Correlation of Antihyaluronidase Titers with Clinical Phase of Rheumatic Fever

The differences noted above warranted a careful examination of the relative sensitivity of serum antihyaluronidase titer in rheumatic subjects to the clinical phases of the disease, in comparison with that of the other tests. This was studied in four ways.

1. *Antibody titer levels in patients with active rheumatic fever as compared with normal children.* The ratio of the mean titers in active rheumatic carditis to the mean normal level was found to be 13.3 in the case of antihyaluronidase, as compared with 3.28, 2.73 and 2.54 for the antistreptolysin, anti-CP and anti-S tests respectively. The actual distribution of titers by frequency of occurrence shows again a greater difference between active rheumatic and normal subjects in the case of antihyaluronidase titers than of the other tests. These data will be presented later, in the section on diagnostic applications of the antihyaluronidase test.

2. *Serial antihyaluronidase titers in the serum of patients showing fluctuations in the activity of the rheumatic process.* Large scale serologic tests were performed in the case of those children who had been studied clinically during sharply defined episodes and reactivations of rheumatic carditis. Since it is impossible to present all of these data, the courses of four patients, typical of the entire group, are presented in Fig. 2.

Fig. 2 shows the results of serial determinations of the titer of the four antibodies, in time-correlation with some of the clinical evidence for the activity of the rheumatic process at the time of collection of the serum. Although there were fluctuations in titer, as one expects in the results of such tests, it is possible to say that the antihyaluronidase titers, represented by the solid black line, showed a somewhat better correlation with the degree of clinical activity than did the other three tests. There was, in general, a greater and earlier fall in antihyaluronidase titer after the subsidence of rheumatic inflammation, and especially a steeper rise in titer at the time of reactivation of the rheumatic process. Even in the case of the antihyaluronidase test, however, titers remained elevated for some time after apparent clinical quiescence had begun.

3. *The fall in titers during the period of decreasing rheumatic activity.* For a more quantitative approach to the question under consideration in this section, all those patients were selected in whom the time of complete subsidence of an episode of rheumatic infection was comparatively sharply defined on clinical grounds, and from whom a specimen of serum had been obtained at that time. For each of these children two groups of sera were examined, one at the height of the active rheumatic episode, and the other at the time when clinical evidence of activity was considered to have terminated. The result of such comparisons of antihyaluronidase and antistreptolysin titers are shown in Fig. 3. In this figure each dot represents the fall in titer for the antistreptolysin test against the fall in titer in the antihyaluronidase test for the serum of one patient studied from the height of rheumatic activity through quiescence. These data are shown in logarithms to the base 2, so that decreases of 1, 2, 3 and 4 units in logarithmic titers mean, respectively, 2-fold, 4-fold, 8-fold and 16-fold decreases in titer. The diagonal line in the chart separates those sera which showed a greater fall in titer in the antihyaluronidase test than in the antistreptolysin test from those sera which showed the reverse, namely, a greater fall in antistreptolysin titer than in antihyaluronidase. The dots falling on the diagonal line indicate those sera showing an equal decrease in titer in both tests.

Fig. 3 shows that of the 48 sets of sera tested, the two titers fell equally in five cases.

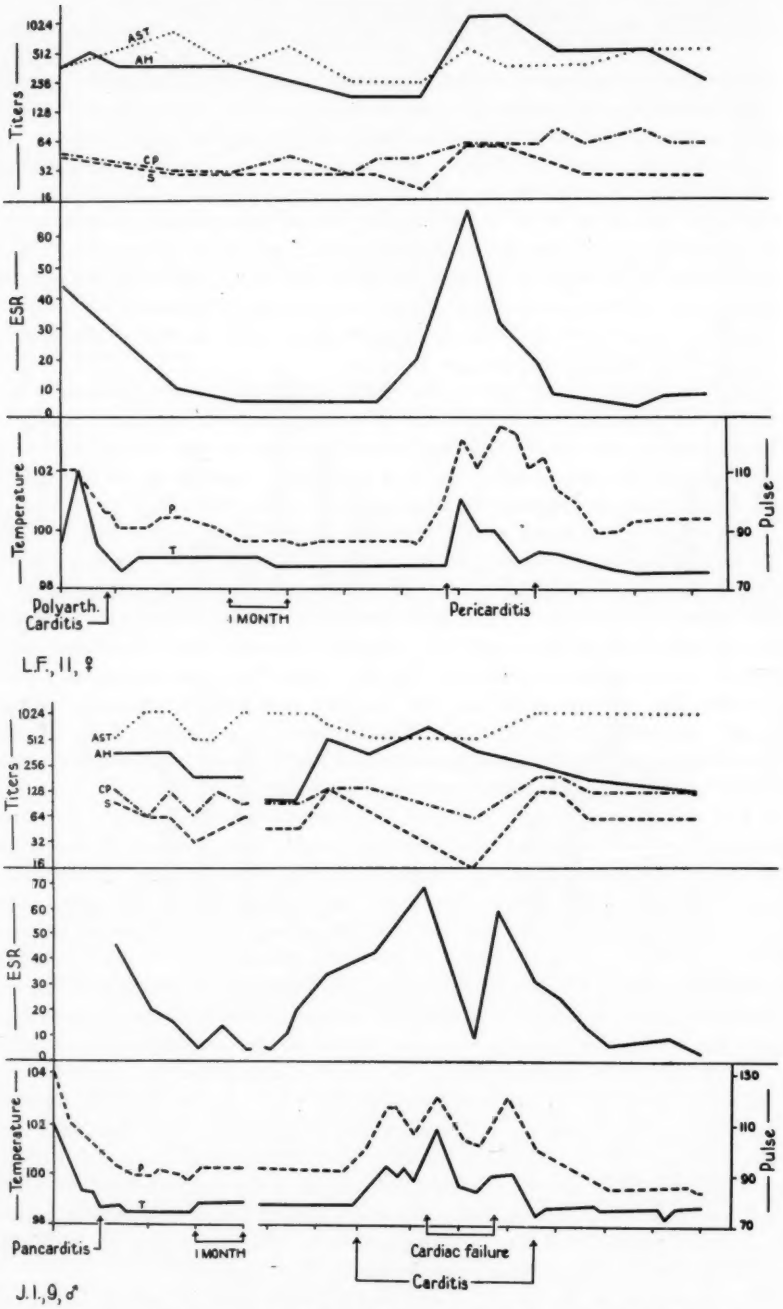
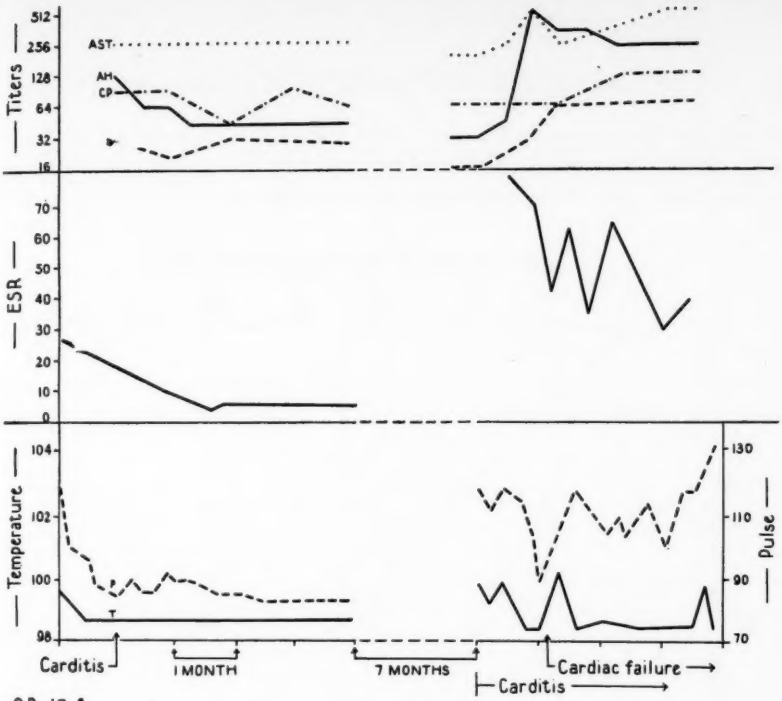
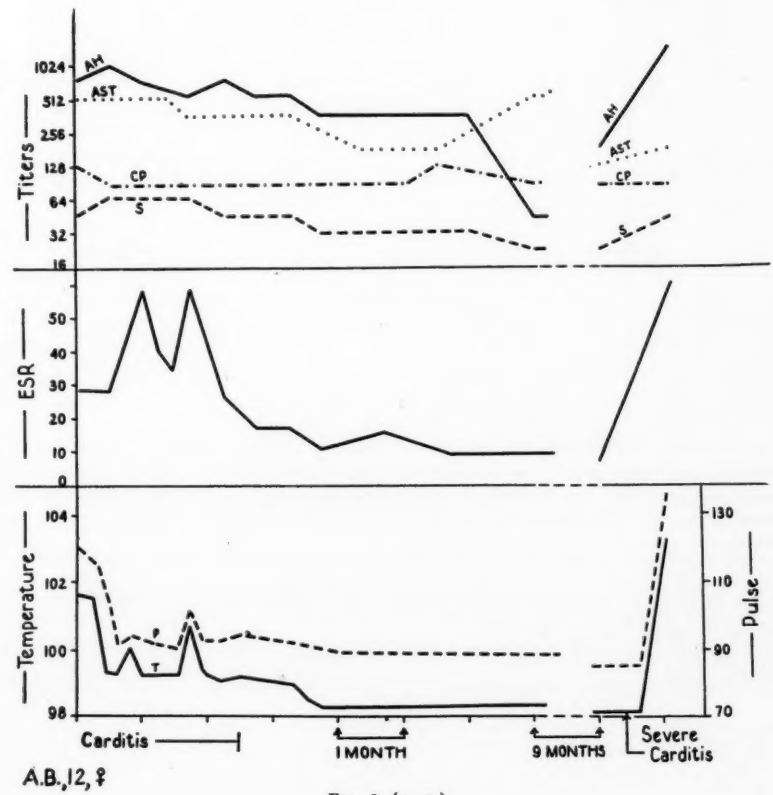


FIG. 2. Correlation between variations in activity of rheumatic process with titers of antihyaluronidase, antistreptolysin, anti-CP and anti-S antibodies.



C.B., 10 ♂



A.B., 12, ♀

FIG. 2 (cont.)

(In two cases, there was no fall in titer during this period by either test.) Of the other sets of sera, the antistreptolysin titer showed a greater decrease in one case, and the antihyaluronidase titer in 40. It is also seen that there were 14 cases in which no fall in

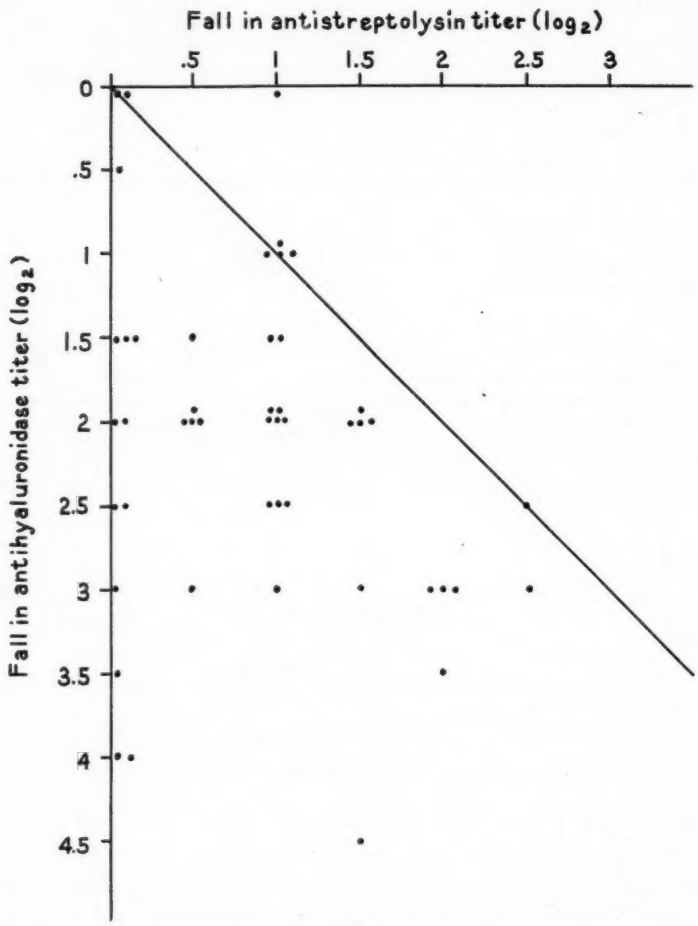


FIG. 3. Fall in antihyaluronidase titer between height of rheumatic activity to termination of that episode, in comparison with corresponding fall in antistreptolysin titer. Each dot represents fall in titer for antistreptolysin test (plotted along abscissa) against fall in titer in antihyaluronidase test (plotted along ordinate) for serum of one patient studied from height of rheumatic activity through quiescence.

antistreptolysin titer occurred during this period of clinical subsidence, as compared with three in the antihyaluronidase test.

4. *Changes in titer at a time of clinical reactivation of the rheumatic process.* There were 22 cases in which unequivocal reactivations of rheumatic carditis occurred while

TABLE II

INCREASES IN TITERS TO 4 STREPTOCOCCAL ANTIGENS IN SERA OF RHEUMATIC SUBJECTS AT TIME OF RECRUDESCENCE OF RHEUMATIC ACTIVITY: RATIO OF TITERS IN ACTIVE DISEASE TO TITER OF PATIENT DURING PRECEDING QUIESCENT PERIOD

	Antihyaluronidase	Antistreptolysin	Anti-CP	Anti-S
RB	4	1.4	1.4	—
EB	16	32	—	2
AB	32	1.4	—	2
RB	8	2	—	2
CB	16	2	1.4	—
FC	4	2	4	4
GD	8	2.8	—	—
GE	2.8	4	1.4	1.4
LF	4	1.4	—	2.8
JF	24	32	4	4
KF	12	5.6	—	2
MH	5.6	—	—	2.8
JI	11.2	—	—	4
TJ	2.8	1.4	2	1.4
LJ	32	2	2.8	2
WL	45	2.8	1.4	4
LM	2.8	—	1.4	—
FM	8	—	2.8	—
JP	8	2	—	—
BP	8	2	—	—
EP	5.6	—	1.4	2.8
DS	8	1.4	2	2.8
Total 22		—=no change		
Mean Ratio of Titers at Height of Episode to That Before	8.80	2.46	1.60	1.88
Percentage of Reactivations for Which No Rise in Titer was Found	0	22.7	41	32
Percentage of Reactivations Showing Less than a 2-fold Rise	0	45	73	41

the patient was under observation, so that it was possible to compare the respective titers before the reactivation with those found during the acute episode. The increases in titer are shown in each case in Table II.

In Table II the greater rise in antihyaluronidase titer at the time of rheumatic reactivation is apparent, and is statistically highly significant. The ratio of the mean of actual titers during the rheumatic reactivation to that preceding the episode is 3.5 times as high for antihyaluronidase as for the highest of the remaining three antibodies. Perhaps most significant of all is the fact that in the data available thus far every reactivation has

been accompanied by a corresponding rise in antihyaluronidase titer, although this is not the case in any of the other three tests.

5. *Correlation between range of antibody titers and the severity of the pathologic process.* In the data presented thus far there has been no division within the group of patients with active rheumatic carditis on the basis of clinical severity of the disease. In an approach to this question, the patients with active carditis were divided into four groups of increasing clinical severity, and a fifth group was added, of rheumatic polyarthritis uncomplicated by carditis. The mean antibody titers to the four antigens in these five clinical groups are shown in Table III.

The data in Table III do not show a satisfactory correlation between mean antibody titer and clinical severity for any of the tests. The greatest progression of titers is shown

TABLE III

MEAN ANTIBODY TITERS TO 4 STREPTOCOCCAL ANTIGENS IN VARIOUS GRADES OF CLINICAL SEVERITY IN RHEUMATIC FEVER

	Number of Cases	Anti-hyaluronidase	Anti-streptolysin	Anti-CP	Anti-S
Rheumatic					
Polyarthritis	18	138	256	78	16
Carditis					
Mild	33	388	248	146	24
Moderate	70	640	256	112	31
Severe	23	276	318	97	34
Fatal	22	276	256	112	18.5

between polyarthritis and carditis of moderate severity in the case of the antihyaluronidase test. Even in this case, however, more severe grades of carditis were not accompanied by higher titers.

DIAGNOSTIC CONSIDERATIONS

1. *Relative frequency-distributions of titers of the four antibodies in the rheumatic and normal groups:* In earlier work, and in the first part of this paper, it was shown that the mean titer of all four antibodies was higher in active rheumatic fever than in the normal population of similar age. For application to the problem of laboratory diagnosis of rheumatic fever, however, it is the relative range of titers, rather than the relative mean titer, which is important. For, regardless of the difference which separates the mean titer found in the rheumatic and normal group, respectively, in the case of a given test, the usefulness of that test for the diagnosis of rheumatic fever is limited directly by the extent of overlapping of the frequency-distribution of titers found in rheumatic patients with those found in normal children. Accordingly, frequency-distributions of titers obtained in these two groups were examined in order to determine whether any one of the tests was substantially more suitable to the laboratory diagnosis of rheumatic fever than the others.

There are technical problems in arriving at a method by which serologic tests can be compared in terms of relative frequency-distributions in a control and an experimental group. The actual concentrations of serum antibodies in populations occur in continuous

distribution, but the technics of serology impose the necessity of conducting measurements in discrete steps, such as dilutions of 1:64, 1:96, 1:128. Thus, in the frequency-distributions such as those shown in Fig. 1, the column height over a given titer does not in reality represent the number of sera which had the concentration of antibody corresponding to that column, but rather those which had a concentration of antibody between that titer and the next step in the titration. For example, in a titration including steps of 64, 96, 128, a computed frequency or, graphically, a height of column of 16% corresponding to a titer of 64 actually means that 16% of the sera tested in that group had 64 or more units of antibody per standard volume, but less than 96. Finally, estimates of the separation of frequency-distributions of serologic titers will hardly ever yield data by which tests can be quantitatively compared, if the calculations are based on the titers actually used in the test. At best, for example, it would be possible to say that a given percentage of all normal sera tested showed titers up to and including, say, 64, whereas another percentage of rheumatic sera had titers of 96 and beyond. While such data present an impression of the degree to which normal and rheumatic sera are separated in a given test, they render impossible an accurate comparison of data on any two tests because of the number of percentages involved.

The problem of quantitatively comparable estimates of separation of rheumatic and normal titers for the respective tests involves, then, the computation for each test of an antibody concentration such that the percentage of normal sera showing antibody concentrations below that value will equal the percentage of rheumatic sera having an antibody concentration above it. That percentage will give a single numerical index of the separation of the two groups of titers for that test, and will be directly comparable to similarly derived indices of other tests. A higher index for a given test would mean greater separation of the distributions of titers between the normal and rheumatic groups, and greater usefulness of the test. An index of 50 would mean that a test is entirely without value for diagnosis, since half of the rheumatic sera would have antibody concentrations above the titer corresponding to the index, and half of the normals below it. A theoretical index of 100 would, of course, be the ideal one, implying infallibility of the given test in the laboratory diagnosis of the disease. Within the range indicated, this index offers a measure of the relative usefulness of a given test.

A method for arriving at such an index, which takes into consideration the factors mentioned two paragraphs above, is as follows:

For the purpose of illustrating application of the method, we may use the data on antihyaluronidase tests in Table IV. The data to be analyzed can be arranged in a manner similar to that in the table. Each column should then be cumulated downward, and for each individual percentage we would substitute the total up to and including that percentage. We then note the sum of the pair of cumulated percentages for each titer. In the case of the lowest titer for which this sum exceeds 100, the two components of this sum are denoted as b and d, for normal and rheumatic distributions, respectively. The two cumulated percentages immediately above these, whose sum has fallen just short of 100, are similarly indicated by a and c, in the same order. The index is then given by:

$$I = \frac{bc - ad + 100\,(a - c)}{a - b + c - d}.$$

It may be noted that this treatment is quite independent of the width of interval of titer employed.

Table V shows the index for the four tests under consideration, and incidentally, the corresponding titer. The most useful of the four tests would appear to be that for antihyaluronidase, since a titer exists above which lie 84.5% of titers found in active rheumatic carditis, and below which lie a similar percentage of titers in the normal popula-

TABLE IV

PERCENTAGE-FREQUENCY DISTRIBUTION OF ANTIHYALURONIDASE AND ANTISTREPTOLYSIN TITERS IN STREPTOCOCCAL AND RHEUMATIC INFECTION

Titer	Antihyaluronidase		Antistreptolysin	
	Rheumatic* Fever	Strep.† Infection	Rheumatic* Fever	Strep.† Infection
<8		19		2
8				
12		1.3		.7
16		2.1		2
24	.8	7.7		.7
32	1.5	4.2		3.3
48	1.5	7.7	.8	3.3
64	.8	10	2.3	10.7
96	2.3	11.3	2.3	9.5
128	6.3	11.3	13.7	20.0
192	6.3	7.7	16	13.5
256	5.5	6.4	26.2	20.9
384	12	4.2	15	4.7
512	20	6.4	16.7	4
768	16.7	.7	3	2.7
1024	6.3		4	2
1536	13			
2048	4			
3072	3			

* 126 patients.
† 149 patients.

TABLE V

INDEX OF RANGE DIFFERENCE (I.R.D.) BETWEEN ANTIBODY TITERS OF NORMAL AND RHEUMATIC CHILDREN TO 4 STREPTOCOCCAL ANTIGENS

	I.R.D.	Corresponding Titer	Titer as Log_2
Antihyaluronidase	84.5	208	7.7
Antistreptolysin	76.7	193	7.6
Anti-CP	73.5	78	6.3
Anti-S	71.5	19	4.25

tion. The second test, in order of usefulness, is the antistreptolysin, with a corresponding index of 76.7.

2. *The qualitative interpretation of streptococcal serologic tests in relation to rheumatic fever.* Since all of the tests under consideration involve antistreptococcal antibodies, and can in no way be said to be specific for the rheumatic process, their significance for a

diagnosis of rheumatic fever must in all cases be interpreted in the light of possible effects of foregoing streptococcal infection in the patient. Unfortunately, antistreptolysin titers may remain almost undiminished in degree for months after a streptoccocal infection, as has been shown in extensive studies by Mote and Jones[24] and others. This has been discussed in the light of the probable causes of this phenomenon: the epidemiology of the streptococcus and the breadth of immunologic reactivity of the hemolysin within group A streptococci.[23] The same difficulty of interpretation would similarly be present in the case of any broadly reactive streptococcal antibody. Under these circumstances, an elevated antistreptococcal antibody titer in a patient suspected of active rheumatic fever can be interpreted as implying the diagnosis of rheumatic fever only if it can be established with certainty that there has been no streptococcal contact of clinically recognizable grade on the part of the patient within at least the past half year. Since this severe limitation applies to all titers in the range of magnitude found after streptococcal infection, it was considered particularly advisable to compare the percentage-frequency-distributions of titers in active rheumatic fever with those found after streptococcal infections. These are shown, for antihyaluronidase and antistreptolysin, in Table IV.

The data in Table IV show that 43% of the 126 patients with active rheumatic fever had antihyaluronidase titers of 768 or more, which is beyond the range encountered after streptococcal infections. In these cases, it was, then, possible to say that the test implied the presence of active rheumatic infection, without qualification in terms of foregoing contact with the streptococcus. In the case of antistreptolysin, however, none of the titers found in active rheumatic fever was outside the range found after streptococcal infection, so that in none of these patients would it be possible to report the likelihood of active rheumatic fever without the condition mentioned above. In the case of any antistreptolysin titer higher than 1024, the laboratory diagnosis of rheumatic infection, could, of course, be made with the same degree of assurance as applies to the 43% of antihyaluronidase titers above 768. It must be noted that the 43% of antihyaluronidase titers in rheumatic fever thus far found to be above the range of those found in the group of streptococcal convalescents is separated from the upper limits of the latter distribution by 1 to 2 twofold steps of serum dilution. In view of the inevitable small variations in potency of enzyme and standardization of such neutralization tests, it is obvious that in practical application one could not expect to realize the full advantage of the theoretical value.

3. *Advisability of plural serologic tests for active rheumatic fever.* Since the data of Table V show that the best of the four tests is far from satisfactory for the laboratory diagnosis of rheumatic fever, the question arises as to whether sufficient advantage would accrue from the simultaneous performance of any two tests to justify the additional work involved. A different set of standards seemed indicated for this analysis of the data, since the performance of plural tests would be justified only by an unequivocal result. Accordingly, a titer was chosen for each test such that approximately 99% of all the titers found in normal children fell below it. This titer, or any higher one, might then, in the case of each test, be considered "diagnostic" of rheumatic fever, with the important proviso concerning foregoing streptococcal infection. The term "diagnostic" is here used only in a quantitative, relative sense because of the proviso mentioned, and because of the probable nonspecificity of these tests to rheumatic fever.

These "diagnostic" standards were found to be respectively, 512, 512, 384, and 96 for the four tests (antihyaluronidase, antistreptolysin, anti-CP and anti-S). They were applied to the data available as follows:

Of the 126 values for antihyaluronidase in active rheumatic carditis, 79 were at least 512, and were therefore higher than the entire range of normal titers. They could, therefore, be considered "diagnostic" of rheumatic fever, in our present state of knowledge (with the exception that 25 of the 79 occurred within the upper limit of titers found in streptococcal infections). The remaining 47 sera were examined in terms of the corresponding antistreptolysin titer. It was found that seven of these sera had antistreptolysin titers in the "diagnostic" range of 512 or above, and the remaining 40 sera, 384 or below. In those seven sera, then, the combination of the two tests led to a definite im-

TABLE VI

COMPARISON OF VALUE OF ANTIHYALURONIDASE AND ANTISTREPTOLYSIN TESTS AS ADJUNCTS TO EACH OTHER IN LABORATORY DIAGNOSIS OF RHEUMATIC FEVER

	Antihyaluronidase		Antistreptolysin	
"Diagnostic"* Threshold	512		512	
Number of Specimens	126		126	
	Number	*Per Cent*	*Number*	*Per Cent*
"Diagnostic" Regardless of Possible Recent Streptococcal Infection	55	43	0	0
"Diagnostic" Provided No Recent Streptococcal Infection	79	63	30	23.5
Below Diagnostic Level	47	37	96	76.5
Of Those Below Diagnostic Level, Above Diagnostic Level By Opposite Test	7	15	55	54.5

* All titers at or above this level are higher than 99% of all found in the normal population. See note on the term "diagnostic" as here used, on page 495.

plication of rheumatic fever (with the usual streptococcal proviso), whereas the antihyaluronidase test alone failed to do so. Of the 40 sera in which the titer by neither test was in the "diagnostic" range, the addition of anti-CP to the group added only three more sera in which any titer was in the "diagnostic" range for that test, and the anti-S only one more. Of the 47 sera below a diagnostic level by antihyaluronidase, then, 36 were not above the corresponding level by any of the three tests as well.

In the case of the antistreptolysin test, 96 of the 126 sera showed titers below the diagnostic level. Of these, 55 were above the corresponding level by the antihyaluronidase test. These data are summarized in Table VI.

DISCUSSION

Comparison of the mean titers in rheumatic and streptococcal infection by the four serologic tests indicates two conclusions: First, the mean titers obtained in all tests are higher in the rheumatic than in the streptococcal group; and, second, this difference is definitely greater in the case of antihyaluronidase than of the other three tests.

1. *The differences in mean antistreptolysin, anti-CP and anti-S titers between rheumatic and streptococcal infections.* The data reported here can to some extent be compared to results which have been reported from other laboratories, with the limitations that, of these three tests only the antistreptolysin has been dealt with in the past and that data

have frequently been presented in forms other than the comparison of mean titers or distributions.

The rather small but consistent difference which we have found between antistreptolysin levels in active rheumatic fever and streptococcal upper respiratory infection are in quite good agreement with several such comparisons in the literature.[25-29] Green,[28] whose data are in the form most comparable to ours, analyzed approximately a thousand sera and found a mean titer of 444 in active rheumatic fever, in comparison with mean titers of 300 and 263 in scarlet fever and streptococcal pharyngitis, respectively. These data, then, are consistent with a somewhat higher mean antistreptolysin titer in rheumatic infection than in streptococcal infection, as was found here.

The differences in mean titer in the case of the antistreptolysin, anti-CP, and anti-S, are so uniform, despite the differences in range of titer and type of serologic test, as to suggest an explanation for the higher titers in rheumatic fever in terms of the contact between the host and the streptococcus as a whole, rather than the reaction of the tissues of the host to the respective antigens. (It is of interest in this connection that several authors have reported levels of streptococcal antifibrinolysin which are, again, higher in rheumatic fever than in streptococcal upper respiratory infection.[29-32])

One possible explanation for this difference would lie in the time relations involved. In these terms, one might suggest that the streptococcus has not been in contact with the tissues of the host for a sufficiently long period, in the case of the third-week bleedings in scarlet fever, to give rise to maximal antibody levels. In rheumatic fever, however, an interval longer than three weeks would usually elapse between the onset of the foregoing streptococcal infection, if any, and the first examination of the patient. In order to test this possible interpretation, serum specimens were collected from a number of the convalescents from streptococcal infection six weeks after the onset of that infection and compared with the sera drawn three weeks earlier. In all three tests the patients who showed no rise in titer between the third and sixth weeks following the onset of the infection comprised the majority of the group. The antistreptolysin titer did not rise during this period in 83% of the group, and in none of the remainder did the increase in titer exceed a twofold difference. The corresponding percentages for anti-CP and anti-S were 58 and 75, respectively.

There findings are, again, in agreement with data recorded in the literature in the case of the antistreptolysin test.[24,26,28,33,34] In the two most extensive of these series, Green[28] found that almost all children with scarlet fever in his series showed their highest antistreptolysin titer during the third week, and Mote and Jones[24] found titers in the fifth to twelfth weeks after the onset of streptococcal infection no higher than those found between the first and fourth weeks.

The factor of time cannot, then, explain the higher titers found in rheumatic fever than in streptococcal disease. Another possible explanation is that rheumatic fever may tend to follow those infections or contacts with Str. hemolyticus which result in higher antibody levels, whether these are due to a factor related to the infecting organism or to the tissues of the host. It should be noted in this connection that this category of streptococcal infections is not necessarily identical with the most severe ones, since it is not possible to indicate at this time the degree of correlation between the clinical severity of streptococcal infections and the general level of antistreptococcal antibodies in the convalescent's serum.

2. *The antihyalurondiase titer in rheumatic and streptococcal infection.* It has been pointed out that the uniformity of the rheumatic-streptococcal differences in mean titers of antistreptolysin, anti-CP and anti-S seems to indicate some factor in the relations between the streptococcus and rheumatic fever. Similarly, the fact that this difference is, in the case of antihyaluronidase, set apart to a significant degree from the closely grouped differences found in the other three tests, calls for consideration of any possible relation between streptococcal hyaluronidase and rheumatic fever.

The possibility that this difference may depend on time relations is not obviated by the discussion of this factor in the case of the other three antibodies, since a difference in rates of production among antigens of an infecting organism might well result in corresponding differences in the time of attainment of maximal serum titers of the corresponding antibodies. Accordingly, sera were collected whenever possible from the convalescents from streptococcal infection six weeks after onset of the disease. Antihyaluronidase determinations were made on these sera, together with the corresponding sera taken three weeks earlier. It was again found that the majority of the group showed no increase in this titer between the third and sixth week; in 83% the antihyaluronidase titer in the sixth week was within a twofold step of that found in the third week. In another group of such convalescents, the mean antihyaluronidase titer was found to be lower 15 weeks after the onset of the acute infection than at the conventional three-week bleeding.

There is, however, another aspect of the time factor which must be considered among the circumstances which could give rise to the phenomenon under discussion. Acute episodes of rheumatic fever are not by any means always preceded by frank streptococcal infections. The foregoing contact with Str. hemolyticus may frequently be so subtle as to be detectable only by serologic evidence. Under these circumstances it is possible that a poor antigen, or one produced in amounts less than optimal for stimulating the production of antibodies, might be more effective after a greater length of time than a larger total amount of antigen liberated in relative profusion for a short time, as in the case of acute bacterial infection. Although such an explanation of the higher antihyaluronidase titers in rheumatic infection may not seem highly probable, it is obvious that every conceivable explanation of this phenomenon must be considered before any suggestion can be entertained of a special role of streptococcal hyaluronidase in the pathogenesis of rheumatic fever.

3. *The correlation of antihyaluronidase titers with the activity of the rheumatic process.* It is difficult to assess quantitatively the changes in antihyaluronidase in their time-relations to the clinical changes in rheumatic fever. Such illustrations as those in Fig. 2 show this correlation to be somewhat better in the case of this test than of the others, but on systematic analysis of all the data, one finds instances of changes in antihyaluronidase titer without corresponding change in clinical status within the period of rheumatic activity, and vice versa. It is the more difficult to judge these relations because of quantitative considerations, such as the sensitivity of the serologic and clinical methods employed and the factors involved in the efficiency of production of antibodies, since it is the latter which we are measuring, rather than the production of hyaluronidase itself. These correlations are, therefore, presented as a part of the natural history of rheumatic infection, and not as data on a possible role of streptococcal hyaluronidase in this disease.

A more quantitative approach is offered by the comparison of serologic titers at the height of rheumatic infections with those found just as those episodes were lapsing into quiescence. Such data are also more significant than a comparison of mean titers of the respective tests in active and inactive rheumatic disease. This is because in any group of patients with inactive rheumatic disease, the time since the termination of the last active infection ranges so widely as to render quantitative judgments impossible. This comparison indicates a better correlation with the clinical course of the disease in the case of antihyaluronidase than of the other antibodies.

An even more refined measure of this correlation is offered by the study of antibody titers at the time of reactivation of rheumatic infection, for not only is the time interval

TABLE VII

MEAN CHANGES IN TITERS OF ANTIHYALURONIDASE AND ANTISTREPTOLYSIN CORRESPONDING TO TRANSITIONS BETWEEN ACTIVITY AND INACTIVITY OF RHEUMATIC INFLAMMATION IN INDIVIDUAL PATIENTS

	Antihyaluronidase	Antistreptolysin	Ratio Between These Mean Changes in Titer, Antihyaluronidase: Antistreptolysin
Mean Ratio of Titer in Active Rheumatic Fever to That Found at Subsidence of That Episode	4.36	1.80	2.41
Mean Ratio of Titer at Height of Recrudescence to That Found in Preceding Period of Quiescence	8.80	2.46	3.58

far shorter, but, in addition, the rate of change in the activity of the rheumatic process is far greater. In these comparisons, the better correlation of antihyaluronidase with clinical developments is again seen on inspection of the data. It is consistent with the evidence for this point that the greater rate of change in the intensity of inflammation which we have at the onset of a recrudescence of rheumatic activity, in comparison with that which obtains during its subsidence, permits a better exhibition of the relative sensitiveness of antihyaluronidase to clinical changes than does the latter. Thus, in Table VII, it is seen that, corresponding to the more rapid clinical change of reactivation, not only are the changes in mean titers greater than during the subsidence of inflammation, but that the degree of this change is relatively greater in the case of antihyaluronidase than of antistreptolysin.

The data on changes in titers at the time of recrudescence may also be examined from another point of view. It will be noted, in Table II, that of the clinical material available thus far, no case failed to show a rise in antihyaluronidase during a reactivation, whereas in the case of each of the other three antibodies, there are instances of reactivation without rise in titer. Further, in the case of each of the other tests, several of the rises of titer are in a ratio of 1.4, or only half a twofold step in dilution, and are therefore of uncertain significance. The rises in antihyaluronidase, on the other hand, were in every case at least one and a half twofold steps, corresponding approximately to a

threefold rise in titer. This finding is of interest not only in terms of streptococcal hyaluronidase, but in terms of the streptococcal theory of rheumatic fever. In the earlier work on streptococcal serology in rheumatic fever, notably the extensive studies of Mote and Jones[24] and Green,[28] it was found that although the majority of patients with rheumatic reactivation showed a corresponding rise in antistreptolysin titer, there were some unquestioned recrudescences which were accompanied by no rise in titer. The data presented here on antistreptolysin are in good agreement with the earlier work, even to the approximate percentage of such recrudescences. Of the newer tests, the anti-CP and the anti-S titers again show similar results. The antihyaluronidase titers, however, rose at the time of each of the recrudescences which we have thus far studied. The application of this new test for an antistreptococcal antibody has, then, resolved an apparent inconsistency between the streptococcal theory of rheumatic fever and the relevant serologic data.

The conditions necessary for the serologic study of a patient before and after the onset of a recrudescence of rheumatic fever are so restricting that the number of such instances is relatively small. Accordingly, it should be borne in mind that although this number of reactivations, 22, was extracted from a wealth of clinical material, it is in a statistical sense a small number, and our experience thus far does not in any way preclude the possibility that instances of rheumatic reactivation without concomitant rise in antihyaluronidase titer will be discovered in subsequent studies. This possibility does not, however, affect the validity of the discussion above.

4. *Serologic titers and clinical severity of the disease.* The data in Table III involve individual groups which are thus far quite small, and clinical criteria which necessarily lack the precision of laboratory measurements. Accordingly, no conclusions will be drawn from such differences as are found in the column of antihyaluronidase titers. Some significance may be attached to the apparent lack of such differences in the case of the other three antibodies, but considerable extension of this work will be necessary before any conclusions can be drawn.

5. *Diagnostic considerations.* Since there is at present no laboratory test specific for rheumatic infection, data have been presented above which could be applied to the evaluation of these four antistreptococcal serologic tests for rheumatic fever. The index of range difference developed above is of limited practical value, since the titer corresponding to the index is too low to permit a useful interpretation of such a titer when it is found. Its value lies in the comparison it affords of the relative usefulness of possible serologic tests in terms of the distribution of titer in normal and pathologic clinical material. In this case the application of the index points to the antihyaluronidase test as the most useful of the four, with the antistreptolysin test second. Since the other tests are both newer and less useful according to this index, they have not been considered further in evaluating an optimal procedure for the laboratory diagnosis of active rheumatic heart disease. Of the antihyaluronidase and antistreptolysin tests, the former is quantitatively the better, and affords the first antistreptococcal serologic test in which any of the titers found in rheumatic fever can be considered diagnostic of that disease in the sense that they exceed the range of titers found after streptococcal infection. The data also indicate that where the streptococcal antihyaluronidase test is available, the addition of the antistreptolysin test has some value in increasing the number of sera in which the laboratory can indicate the probability of the presence of active rheumatic infection.

It must at all times be borne in mind that the application of these tests to the diagnosis of active rheumatic fever is severely limited by several considerations. These considerations will, in fact, apply to a greater or less extent to all tests which measure antibodies to streptococcal antigens. First, the antistreptococcal antibody titer found on testing must be distinguished from those found in the presumably normal population on a quantitative basis alone, and the presumably normal range is subject to the variations in the epidemiology of Str. hemolyticus. Second, the streptococcal antigens used in these tests are not only, to the best of our current knowledge, not specific to rheumatic fever, but, what is more, are specifically related to a human pathogen, Str. hemolyticus. This factor involves a more severe limitation on the interpretation of these tests and one which may be quantitatively altered by variations in the virulence and antigenicity of the infecting streptococcus. Thus, for example, the frequency with which we have found the respective tests to satisfy certain criteria represents our experience thus far, and may in some cases be somewhat altered with further use of these tests here and elsewhere. Of the available antistreptococcal tests, then, our data show that the antihyaluronidase test is the best one to apply to the laboratory diagnosis of rheumatic fever, but it is obvious that even this test is far from being satisfactory in any absolute sense.

Summary

Titrations of antibodies to four streptococcal antigens have been carried out in the sera of patients with rheumatic fever and of convalescents from streptococcal infections. These antigens are the hyaluronidase, the hemolysin, and two somatic fractions, the cytoplasmic particles and supernate proteins.

Mean titers to all of these antigens were elevated in both rheumatic and streptococcal infection. The mean titer was somewhat higher in rheumatic than in streptococcal infection in the case of three of these antibodies. In the case of the fourth, antihyaluronidase, this difference was considerably greater.

The antihyaluronidase titer showed better correlation with changes in the activity of the rheumatic infection than did the other tests. There was, however, no striking correlation between this titer and the severity of the illness.

Application was made of these findings to the problem of laboratory diagnosis of rheumatic fever by streptococcal serology. A method is presented for assessing the relative usefulness of such tests in terms of the distribution of their titers in this disease and in health. By this method the antihyaluronidase test was found to be most useful of the four.

The comparative diagnostic value for rheumatic fever was studied in the case of the antihyaluronidase test, the antistreptolysin test, and of combinations of both tests.

Acknowledgment

We are indebted to Dr. A. C. La Boccetta for permission to obtain specimens of serum of patients with scarlet fever in the Philadelphia Hospital for Contagious Diseases.

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SPANISH ABSTRACT

Estudios en la Relación del Estreptococo Hemolítico a la Fiebre Reumática. VI. Comparación de Antihialuronidase Estreptocócica con Anticuerpos a otros Antígenos Estreptocócicos en el Suero de Pacientes con Fiebre Reumática e Infección Estreptocócica aguda.

Sueros obtenidos de convalescientes de infecciones estreptocócicas y de pacientes con fiebre reumática aguda fueron ensayados para anticuerpos a cuatro antígenos estreptocócicos. Estos antígenos son la hialuronidase y la hemolisina, las que se derivaron de la parte flotante de los cultivos estreptocócicos y dos fracciones, las partículas citoplasmáticas y las proteínas flotantes; preparadas de la célula estreptocócina.

Se halló que los títulos medios de todos estos antígenos fueron elevados en ambas infecciones—la reumática y la estreptocócica. En el caso del título antiestreptolisino así como en los títulos de partículas citoplasmáticas y proteina flotante, el título medio fué un poco más alto en la infección reumática que en la infección estreptocócica. Sin embargo, el título medio antihialuronidase que se encontró en el grupo reumático fué considerablemente más grande que el que se halló en el grupo de convalescientes estreptocócicos. Se trata el posible significado de este descubrimiento de un punto de vista de etiología y diagnosis en la fiebre reumática.

1740 Bainbridge St.

ANTEPARTUM DIAGNOSIS OF CONGENITAL ANOMALY OF THE HEART

Case Report with a Review of the Literature

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THE recognition of congenital anomalies of the heart of the fetus has received scant mention in medical literature. Because such a condition was observed and correctly diagnosed antepartum, this report of the case should be of interest.

Hyman[1] states that the condition may not be noted because enough time is not devoted to adequate fetal cardiac auscultation. Other aspects of the routine examination are regarded as more important and to detect the presence or absence of the sounds of the fetal heart usually suffices.

The incidence of congenital heart disease declines with advancing age, especially the more severe lesions which are incompatible with life beyond the first weeks or months following birth. Clinical evidence of congenital heart disease has been noted in 0.3% of newborn infants and in from 0.05% to 0.15% of school age children. Maude Abbott,[2] in 3,633 autopsies of all age groups, recorded 43 cases (1.2%) with congenital anomalies of the heart.

Perusal of medical literature of the past hundred years shows that Massman,[3] in 1854, was the first to record the recognition of an unusual fetal cardiac murmur; he suspected a congenital anomaly of the heart, and this diagnosis was confirmed at autopsy. Barth,[4] in 1880, likewise described a case which was confirmed at autopsy.

Padgett,[5] in 1894, the first American to record such a diagnosis, believed that he heard the murmur of mitral valvular disease in a fetus and his suspicion was substantiated at autopsy. Others reporting similar cases included Bellot[6] and Andry and Lacroix.[7]

Hoehne,[8] from a study of his own case and seven others collected from the literature, proposed three criteria for the diagnosis of fetal congenital cardiac lesions: 1. There is a murmur rough in character, of constant duration and intensity, but not synchronous with the maternal pulse. 2. For the most part, there is a constant defect in both heart sounds; usually the first and occasionally only the first sound is heard. 3. The murmur is heard over the entire abdomen of the mother with greatest intensity in the area where the fetal cardiac sounds are heard best.

During studies of routine fetal phonocardiograms in 31 cases, Sampson and others[3] reported one case of fetal congenital anomaly of the heart. Dipple[9] made a comprehensive review of the literature and added two cases of his own, each having an interventricular septal defect, a patent foramen ovale and a patent ductus arteriosus. One of these had, in addition, marked stenosis of the pulmonary artery, with marked right ventricular hypertrophy and a rudimentary left ventricle. The other case also had a stenosis of the isthmus of the aorta.

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Thomson and Drummond[10] reported nine cases of congenital anomalies of the heart that were associated with other deformities in three instances. These included hare lip, cleft palate, malformation of the external ear, horseshoe kidney and imperforate anus. Another patient was a mongoloid idiot. Roberts[11] reported the case of an infant with congenital anomaly of the heart correctly diagnosed before birth, born to a mother who had congenital anomaly of the heart with severe cardiac failure.

At the present time apparently fewer than 20 cases of congenital anomalies of the heart, suspected in utero and confirmed after birth, either clinically, pathologically, or both, have appeared in the medical literature since 1854. To this the authors wish to add an additional case wherein there were numerous other congenital anomalies.

FIG. 1. Front view, general body contour.

FIG. 2. Profile, facial and extremity defects.

REPORT OF CASE

Mrs. H.R., age 39 yrs., white, para 12, gravida 20, had been in regular attendance at the prenatal clinic since she was 4 months pregnant. The first trimester was uneventful with no illness of any kind. Because of her large family, the mother did not feel it necessary to seek medical attention prior to the fourth month of her pregnancy.

She had been delivered of 10 viable children, 9 of whom were living and well and one of whom died in infancy. Seven spontaneous and two induced abortions dotted the history.

Her general physical condition was good. The prenatal course was uneventful except for a mild pre-eclamptic state. The blood Wassermann test was negative. A moderate hypochromic anemia persisted throughout gestation despite apparently adequate iron therapy. Urinalyses were negative. The blood pressure ranged from 112/60 to 140/70 mm. Hg. The weight gain was only 5.4 kg. Normal fetal cardiac sounds were heard at her first visit to the clinic and at each subsequent examination.

After admission to the hospital she was delivered spontaneously of a living female infant, born about three weeks prematurely, which showed multiple anomalies. (Figs. 1 and 2.)

At the time of admission, four hours before delivery, no note was made as to fetal cardiac sounds. However, when she was examined by one of us (B. H. B.) an hour later, loud, harsh fetal cardiac sounds were heard. Also a noisy, blowing, machinery-like, systolic murmur was detected over the entire left abdomen which was different from the uterine or placental souffle. An anomaly of the heart was suspected. The infant's cardiac rate was 180/min. This rapid rate persisted throughout labor and delivery, during which time the maternal cardiac rate ranged from 88-92/min. The infant breathed spontaneously.

Immediately following delivery, owing to respiratory distress, the infant was given 0.5 cc. of pyridine-B-carboxylic acid diethylamide (Coramine—Ciba) intramuscularly. Alpha-lobelin, 1.0 cc., was administered subcutaneously within 20 minutes of birth. Oxygen, 5 l./min., was started and continued by the box method until death 36 hours later.

The same loud, harsh, blowing systolic murmur was heard during life, but with a diastolic component over the entire precordium, and a systolic thrill was palpable. Moderate cyanosis was present. These findings confirmed the antenatal diagnosis of congenital anomaly of the heart, probably an interventricular septal defect and a patent ductus arteriosus. X-ray films were not obtained because of the infant's condition.

An autopsy revealed the following anomalies:

1. Congenital anomaly of the heart with interventricular septal defect; quadricuspid aortic valve; a common pulmonic and aortic artery; patent ductus arteriosus; patent foramen ovale.
2. Ptosis of left adrenal gland and left kidney; an anomalous blood supply to left kidney arising from left common iliac artery.
3. Bicornuate uterus with separate cervix for either side.
4. Malrotation of intestinal tract.
5. Congenital anomalies of the external ear.
6. Cleft palate.
7. Small tongue with frenulum attached to anterior tip; marked micrognathia.
8. Posterior dislocation of right hip.
9. Maldevelopment of right femur.
10. Left equinovarus, right equinovalgus.

Comment

A case is reported of congenital anomaly of the heart which was diagnosed shortly before birth and the diagnosis confirmed during life and at autopsy. The infant, female, was the twentieth pregnancy, and had numerous congenital anomalies in addition to the cardiac lesions.

It might be that a relationship exists between rapid successive pregnancies and congenital anomalies. An increase in the frequency of congenital anomalies in the offspring of women nearing the climacteric has long been a matter of conjecture; such a relationship has been discussed in cases of mongoloid idiocy.

Acknowledgment

The authors wish to acknowledge the assistance of Dr. Paul Kratz, now on active duty with the U. S. Navy. Dr. Kratz heard the fetal cardiac murmurs before and after birth.

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SPANISH ABSTRACT

Diagnosis Antepartum de Anomalia Congenita del Corazon

Se presentan un informe de un caso y un análisis de la literatura.

Una mujer blanca, 39 años de edad, para 12, gravida 20, principió a asistir a la clínica prenatal a los cuatro meses de embarazo. En el primer trimestre no pasó nada, no hubo enfermedad de ninguna clase. La historia pasada, con la excepción de la fiebre escarlatina y amigdalitis en la niñez y una sospecha infundada de tuberculosis fué negativa. La condición física era buena. La paciente había tenido varios abortos naturales y abortos incitados. Nueve niños viven y están bien.

El funcionamiento del corazón fetal durante el primer exámen y visitas subsecuentes era normal, hasta una hora después de la admisión durante el parto activo. En ese momento se notó un murmuro sistólico, parecido al ruído de una máquina, en todo el abdomen izquierdo, no síncrono con el soplo uterino o de la placenta. La proporción del corazón fetal era 180/min. con el pulso materno de 88-92. Se usaron varias terapias después del nacimiento, pero con poco resultado y el infante fué mantenido bajo oxígeno constante hasta su muerte, 36 horas después del nacimiento.

Después del nacimiento normal, el infante tuvo el mismo tipo de murmuro que se oyó antes del parto, con un componente diastólico y un estremecimiento sistólico palpable. Se presentaron múltiples anomalías congénitas externas.

Al hacer la autopsia se encontró un corazón congénito con defecto septal intraventricular, válvula aórtica cuadricúspide, una arteria aórtica y pulmónica común, canales acteriosos abiertos y aberturas ovales, confirmando nuestra sospecha antenatal de defecto septal intraventricular y canales acteriosos abiertos. También se encontraron otras múltiples anomalías de quijada, oído, fémur derecho, paladar, tracto intestinal y conducto génito-urinario.

6247 Brookside Blvd.

MULTIPLE HEMORRHAGIC HEPATOMA (L'ESPERANCE)

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Trenton, N.J.

TUMORS of infants present striking variations from those of adult forms.[1] While hepatomas constitute a rather numerous group of tumors which are highly malignant and rapid in growth, rare types of this tumor are considered worthy of record. Although, during a three year period in New York City, deaths of children from neoplastic diseases exceeded those from all forms of tuberculosis,[2] the incidence of primary carcinoma of the liver in childhood is not frequent. Nelson[3] found only 13 cases in a review of 1,538 cases of carcinoma in children. Steiner[4] recorded 77 cases in children under 16 years of age, of which 53% were in infants under two years. Hepatic neoplasms are more common in males, the ratio of this tumor in adults being seven males to three females.

The first abnormality noted by the parents is usually the presence of an abdominal mass. It may appear suddenly and show metastasis early, and only prompt clinical study and early surgical intervention gives a chance of hopeful prognosis.

DIFFERENTIAL DIAGNOSIS

A mass in the right upper quadrant in an infant should suggest a neuroblastoma, an embryoma (Wilm's tumor) of the kidney, or a tumor of the liver. Neuroblastoma or sympathoblastoma is characteristically a tumor of infants and children, arising from the sympathetic nervous system and usually primary in the adrenal gland medulla. It frequently extends across the midline and displaces the kidneys downward. Metastasis to the liver, orbit and skeleton occur early.

An embryoma of the kidney gives a similar picture. Metastasis to the lungs and brain are common. A pyelogram will show that the tumor usually displaces the kidney downward and outward.

CASE REPORT

This patient was a white female infant of five months, one of ten siblings, four of whom were living at the time this case was studied. She was brought to the Tumor Clinic of Mercer Hospital for diagnosis. The mother noted upper abdominal prominence when the infant was three months of age. Physical examination revealed a smooth, firm mass in the right infracostal area extending below the level of the umbilicus. Its most dependent part presented a rounded area 5 cm. in diameter, softer than the rest of the mass. The left border of the mass diminished in size in an oblique pattern from below upwards. The sharp edge of the spleen was palpable under the left lateral costal margin (Plate I).

A pyelogram (Plate I) of the left kidney showed the lumen and position of the kidney to be normal. The right kidney was displaced downward, but the lumen seemed to be normal. It was concluded, therefore, that an embryoma of the kidney was not likely. Due to the general configuration of the mass which appeared to be a markedly enlarged liver shadow (Plate II), and since the right kidney was not displaced outward, as it frequently is by a large embryoma, it was concluded that

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PLATE II. Lateral roentgenogram of upper abdominal tumor.

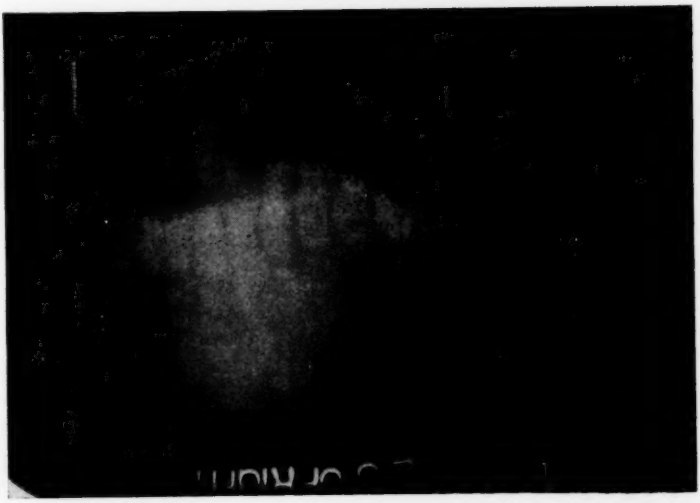

PLATE I. Antero-posterior abdominal pyelogram.

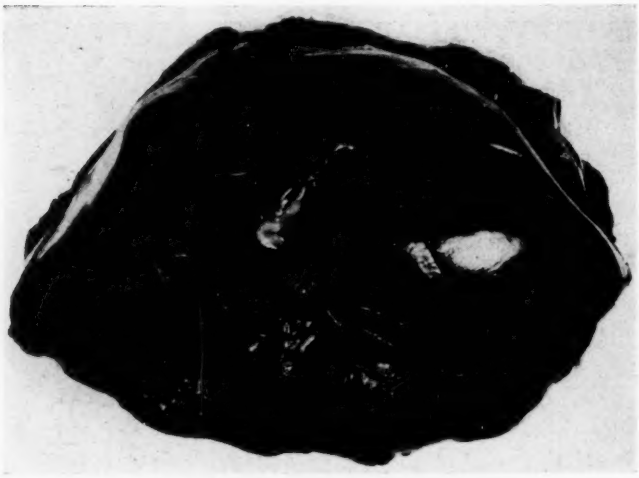

PLATE III. Liver, absence of left lobe involvement.

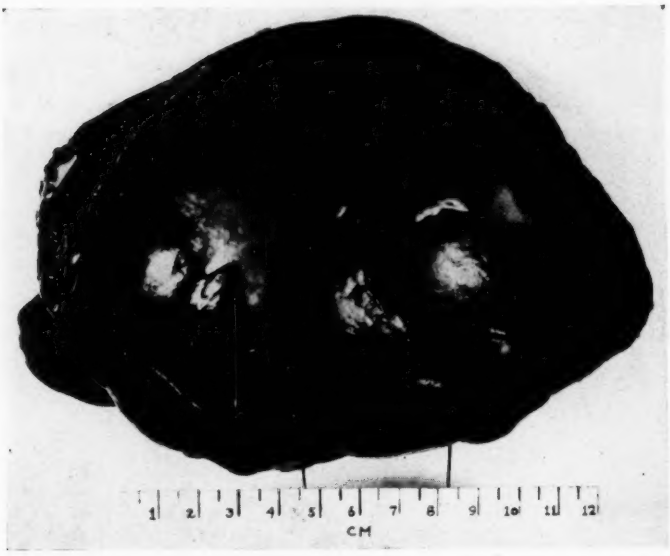

PLATE IV. Gross appearance of right lobe, nodularity, hemorrhage and surface necrosis of tumor.

the tumor was in the liver. No metastases were demonstrable on survey roentgenograms of either the lungs or skeletal system.

Pertinent clinical laboratory findings revealed the following:

Albuminuria	40 mg./100 cc.	Blood Sugar	90 mg./100 cc. blood
Secondary anemia		Urea Nitrogen	30 mg./100 cc. blood
Hgb.	8.6 gm./100 cc. blood	Total Protein	8 gms./100 cc. blood

PLATE V. Cut surface of hepatoma, vascularity, necrosis and fibrous trabeculation of tumor.

RBC count	3.5 million	Albumin	6 gms./100 cc. blood
WBC count	15.6 thousand	Globulin	2 gms./100 cc. blood
Differential count		Icterus Index	3 units
Neutrophiles	46%	Hanger's test	Plus 1
Lymphocytes	42%	Kahn and Kolmer	Negative
Monocytes	5%	Prothrombin Time	Normal
Eosinophiles	6%		
Basophiles	1%		

Surgical exploration was done for the purpose of definitive diagnosis and possible excision. A biopsy of the liver parenchyma was obtained. This established the diagnosis of hepatoma. The child lived an additional 34 days after surgical exploration and expired at the age of 6½ months. Ascites never developed. Postmortem examination confirmed the antemortem diagnosis and was productive of the additional facts that the hepatic involvement by tumor tissue was confined entirely to the right lobe of the liver and that the growth of the tumor mass had produced a left lateral scoliosis of the thoraco-lumbar vertebra. Plate III confirms the absence of involvement of the left lobe of the liver. Plate IV shows the gross appearance of the tumor, and Plate V illustrates the markedly hemorrhagic and necrotic appearance of the cut section.

Grossly the liver measured 16 x 12 x 9 cm. and weighed 1100 gm. The tumor was confined to the right lobe of the liver. No metastases were demonstrable.

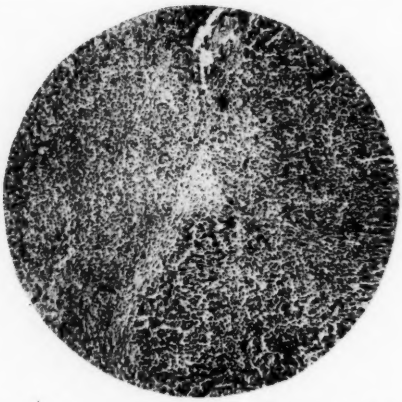

PLATE VI-A. Photomicrograph X100, fibrous trabeculae, vascularity and giant cell formation.

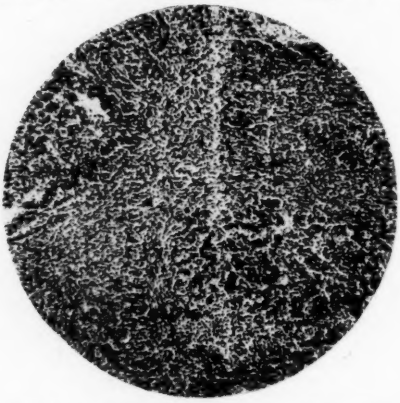

PLATE VI-B. Photomicrograph X100, pseudo-peritheliomatous architecture.

PLATE VII. Photomicrograph X100, necrosis and vascularity of tumor.

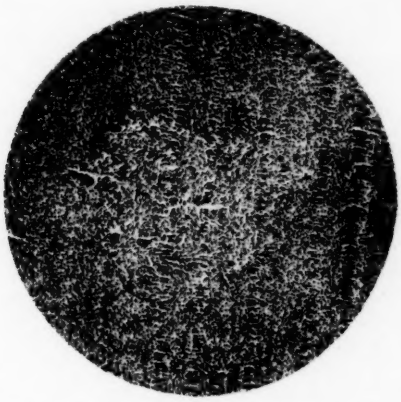

PLATE VIII. Photomicrograph X100, spindle cell pattern, resembling sarcoma seen in areas of tumor.

PLATE IX. Photomicrograph X100, eosinophilic nodules resembling bone seen in areas of tumor.

PLATE X. Photomicrograph X100, collagenous reaction of bone-like areas to modified Masson's trichrome stain.

Histologic studies of the tumor tissue revealed all of the characteristic classical findings of hepatoma; namely, Plate VI-A, tumor giant cells, and Plate VI-B, a pseudo-peritheliomatous structure, with intense vascularity and necrosis (Plate VII) and a sarcomatous spindle-cell pattern in some areas (Plate VIII).

A most interesting feature of the histologic study was the finding of nodules of deeply eosinophilic staining material which, under hematoxylin and eosin stain, were not unlike bone (Plate IX). However, with a modified Masson's trichrome stain these nodules presented a deep green appearance and are therefore considered as collagenous material (Plate X).

This tumor is similar to those originally described as a primary multiple hemorrhagic hepatoma by L'Esperance.[5] The features of this tumor are a peritheliomatous appearance with large or small cuboidal granular cells surrounding capillaries, and large areas of hemorrhage and necrosis as well as areas resembling large spindle cell sarcoma. Ewing[6] regards this as an atypical form of hepatoma. The condition is of sufficient rarity to justify this report for the purpose of record and illustration of the gross and histopathologic changes encountered. The case has been registered with the Army Institute of Pathology as Accession No. 206654.

Summary

A case of multiple hermorrhagic hepatoma of the liver in an infant of five months is reviewed with illustrations of the gross and microscopic pathology.

Hepatomas of infants differ somewhat from those seen in adults.

In the light of our findings, descriptions of bone in hepatic neoplasms should be accepted with reservations.

Acknowledgment

The authors wish to acknowledge the review of this material by Dr. R. Philip Custer, Director of Laboratories, The Presbyterian Hospital, Philadelphia, Pa.

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Spanish Abstract

Hepatoma Hemorrágico Múltiple (L'Esperance)

Un infante de cinco meses de edad, blanco, hembra, presentó una masa tumor en el cuadrante superior derecho del abdomen. Con la excepción de esto el exámen físico fué normal, y los estudios de laboratorio hechos no proporcionaron información adicional. Los descubrimientos clínicos sugerieron un neuroblastoma, tumor embrioma, o un tumor del hígado. Los estudios roentgenográficos excluyeron todo embrioma. La laparotomía exploratoria reveló un tumor primario en el hígado encerrado en el lóbulo derecho. El infante sucumbió y el exámen después de la muerte demostró que no habían lesiones metastáticas. Los estudios histológicos del tejido del tumor revelaron que era un hepatoma hemorrágico múltiple (L'Esperance). Se registró el caso con el Instituto de Patología del Ejército. Las fotografías de las características gruesas e histopatológicas fueron presentadas. Las áreas histológicas dentro del tumor que parecían ser hueso bajo manchas de rutina se mostraron por la mancha tricromia de Masson que debe componerse de tejido colágeno. Se deben aceptar con cuidado las manifestaciones de que el tejido óseo está presente en hepatomas, en vista de los descubrimientos en este caso. Es necesaria la temprana exploración quirúrgica.

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Panel Discussion

THE ADRENAL GLAND IN HEALTH AND DISEASE

By A. WILMOT JACOBSEN, M.D., *Chairman,* GEORGE F. KOEPF, M.D., NATHAN B. TALBOT, M.D., AND LAWSON WILKINS, M.D.

INTRODUCTION

Chairman A. Wilmot Jacobsen, M.D. (From the Department of Pediatrics, University of Buffalo School of Medicine, Buffalo, N.Y.): About 400 years ago Eustachius discovered the adrenal glands. It is interesting that a period of almost 300 years intervened between his original description and identification of these organs and their recognition as important clinical and physiologic entities by Addison. During those three centuries many fantastic theories were elaborated concerning their function ranging from the idea that they were mere space fillers to one which suggested that they diverted blood from the kidneys in order to avoid excretion of urine by the fetus.

Following Addison's beautiful description of the disease known by his name, great impetus was given to the study of the physiology of the adrenals and many data accumulated. And yet one of the best text books of physiology in use 50 years ago written by Austin Flint, contains the following surprising paragraph summing up the current knowledge of the adrenal gland:

"The suprarenal capsules are not essential to life. They may be removed from animals and the operation apparently has no remote effects. It is not established that the changes in the adrenal capsules seen in Addison's disease stand in a causative relation to the discoloration of the skin or to the constitutional disturbance. Investigations into these diseased conditions have developed little or nothing of importance concerning the physiology of the suprarenal capsules."

Indeed only in recent years, with the development of precise biochemical technics, has their true importance come to be appreciated. Thus while cases of actual disease of the adrenals are relatively rare, we see in the unraveling of the knotty problem of adrenal physiology an opening for the understanding of the functions of other endocrine glands and of biochemical problems in general.

Endocrinology as we know it today is a young science—yet one endocrinologic library already contains over a quarter of a million references—with additional publications appearing at the rate of 5,000 per annum. And a glance at the cumulative index will show that the largest single group of these recent additions concerns the adrenals.

From the Annual Meeting of the American Academy of Pediatrics, Atlantic City, N.J., Nov. 20-21, 1948.

So varied and widespread are the demonstrable effects of adrenal secretions that if one had a full understanding of adrenal physiology he would also have a fairly complete knowledge of all physiology. For even a partial list of these effects includes adrenal control of general, protein, carbohydrate and lipid metabolism, electrolyte balance, heat regulation, circulation, other endocrine glands, somatic growth, lymphatic and respiratory system, muscular strength, sexual development and the sexual cycle, renal action, lactation, and immune response. And finally its key role in the recently expounded general-adaptation-syndrome, and hence in the reaction of the organism to every stress and every infection it encounters, as well as in the long list of "wear-and-tear maladies" of which 50% of our population is destined to die.

Let me quote from the works of a medical man named "Senac" who wrote as follows exactly 200 years ago:

"The mind is not great enough and life is too short to embrace all anatomy. In spite of all the help of our predecessors it is hardly possible for one man to develop exact knowledge of a single viscus."

Bearing in mind the words of this wise physician we have brought here this afternoon not one but three experts in the field of adrenal physiology who between them know all (or almost all) there is to know about this viscus.

The Role of the Adrenal Cortex in Stress and Strain

George F. Koepf, M.D. (Associate in Physiology and Instructor in Medicine, University of Buffalo School of Medicine): According to the late physiologist, Cannon, man is endowed with numerous homeostatic mechanisms which enable him to exist with remarkable efficiency in his chosen surroundings. To think in terms of the total processes involved in the mechanism of existence of a complicated organism, such as man, is indeed difficult. To piece together the intermediary physiologic processes with their many ramifications, however, staggers the imagination.

When man is placed under adverse environmental conditions or "beset by disease," the need for readjustment of many physiologic processes becomes apparent. Furthermore, when exposed to these circumstances the individual may be said to be under stress or strain. Ability to tolerate or adjust to these adversities might be called resistance, a term which sane biologists have dodged and sidestepped for many years.

It has been suspected for the better part of a century that the adrenal glands have something to do with resistance to stress and strain. Addison, in his classical description of adrenal-cortical insufficiency in man, recorded that lymphatic tissue hyperplasia and general languor and debility were exhibited by his patients. Incidentally, sudden death and unfavorable reactions to infections are still commonly noted in patients with Addison's disease. Similarly, it has been repeatedly noted that adrenalectomized animals react adversely to various types of stress or strain (such as anoxia, infection, cold, heat and drugs).

The adrenal cortex is not the only important endocrine gland, organ or tissue involved in the adjustment or response of the total organism to its environment. Perhaps, more thought has been directed toward the adrenal gland than other organs in this respect because of the mass of experimental data which has been accumulated to show the fundamental role the adrenal cortex plays when the body is placed under stressful conditions. As will be detailed later, however, the anterior pituitary gland is involved in a major and, what might be termed, more fundamental role in stress mechanisms. The entire body, of course, enters into the response to stressful stimuli.

A Homeostatic Mechanism?

With the availability of purified adrenocorticotrophic hormone (ACTH) obtained from the anterior pituitary an opportunity to move one step nearer to the understanding of the mechanisms involved in stress presented itself. Long and Sayers and Sayers demonstrated that both the cholesterol (which may be the precursor of corticosteroids) and the ascorbic acid content of the adrenal gland of rats was diminished following the injection of ACTH or following exposure of the rats to cold. The decreases in adrenal cholesterol and ascorbic acid which occurred after exposure to cold could be prevented by pretreatment with adrenal cortical extract but similar decreases in the ascorbic acid content of the adrenals following the injection of ACTH were not prevented by pretreatment with adrenal cortical hormone. Sayers interpreted this as an indication that the adrenal cortical hormone

inhibits the production of pituitary ACTH. This conclusion has been strengthened by the results of Patt et al., who demonstrated that the decrease in adrenal gland cholesterol noted in stress does not occur after hypophysectomy. Recently, Ingle et al. were unable to detect any effects of ACTH on the regulation of carbohydrate metabolism other than those mediated by its ability to stimulate the adrenal cortices. Sayers thus presents evidence favoring the existence of a homeostatic type of regulation of the secretion of adrenal cortical hormone and involving the anterior pituitary gland in a manner similar to its control of thyroid hormone secretion. According to his theory, under acute stressful conditions the tissue cells utilize more adrenal cortical hormone and, as a result, the blood level of adrenal cortical hormone decreased. Inasmuch as the adrenal cortical hormone inhibits ACTH production by the anterior pituitary gland, a fall in the blood level of adrenal cortical hormone causes the anterior pituitary to secrete a greater-than-normal amount of ACTH. The increased ACTH stimulates the adrenal cortices to produce more hormone and the deficient blood level of adrenal cortical hormone is thus relieved.

Sayers has also shown that 11 or 17 oxycorticosterones are much more efficient in inhibiting pituitary ACTH production than desoxycorticosterone or progesterone. Thus the adrenal steroids which inhibit the pituitary are those which have been better known for their marked influence on carbohydrate metabolism (stimulation of gluconeogenesis).

Acute Stress

Several years ago, we exposed many groups of rats to acute anoxia assuming the situation to be representative of one type of reproducible stress. Attempts were made to study the effects in terms of adrenal cortical function. As an example of some of the immediate effects, it was noted that the liver glycogen at the end of a 24 hour fast of normal rats in an atmosphere of 10% oxygen (379 mm.Hg barometric pressure) was extremely high (almost 2%) as compared to the near zero levels of control (barometric pressure of 760 mm.Hg) fasted animals. Removal of the adrenal glands prevented this effect from taking place but treatment with adrenal cortical extract caused the adrenalectomized rats to react normally. Blood sugar levels were also increased in the normal but not in the adrenalectomized rats exposed to the anoxic atmosphere. If these results are interpreted in terms of Sayer's hypothesis it would appear that the stress of anoxia diminished the amount of circulating adrenal cortical hormone temporarily. Because of this, the inhibition of the secretion of ACTH by the anterior pituitary was lessened and greater quantities of ACTH were produced. The increased ACTH stimulated the adrenal cortices to produce excessive amounts of adrenal cortical hormone. Increased gluconeogenesis resulted, and was reflected in increased stores of liver glycogen and increased blood sugar levels.

Further evidence that in stressful conditions the adrenal cortices secrete increased amounts of hormone has been presented by Venning and her co-workers in experiments on human subjects. Using the ability of urinary extracts to increase liver glycogen as an index of cortico-steroid excretion, they have reported increases in the excretion of "glycogenic corticoids" in men performing exercise, in pregnancy and in patients with Cushing's syndrome. Conversely, they found that disorders in which the secretion of the adrenal cortices and/or the anterior pituitary gland is diminished, the excretion of the glycogenic substances in the urine is diminished. From this evidence it follows that in humans the increased excretion of these glycogenic substances noted in stress is probably an indicator of increased production of adrenal cortical hormone.

Numerous experimentalists have attempted to gain insight into the nature of the lymphocytic tissue regression noted when excessive amounts of adrenal cortical hormone are secreted or injected. Lymphopenia not only results when adrenal cortical hormone is injected, but also following acute stress. Pincus and co-workers have used the degree of lymphopenia as an indication of adrenal cortical function in human subjects and experimental animals.

Dougherty and White have shown that in rabbits and mice, the injection of ACTH or certain C 11 oxygenated steroids caused rapid lymphocytic dissolution in the spleen, thymus and lymph nodes with a resultant failure of lymphocytes to appear in the circulating blood in adequate numbers (lymphopenia). Injection of ACTH in adrenalectomized mice, however, failed to produce the lymphocytolysis. White and Dougherty have, in addition, more recently presented evidence that increases in serum gamma globulin after ACTH injection are due to the release of this protein from lymphocytes. Moreover, they were able to demonstrate an increase in the effectiveness of specific immunization in

rabbits by the injection of ACTH or adrenal cortical extract. As the injection of ACTH was not effective in this respect in adrenalectomized animals but adrenal cortical extract was, it would appear that the adrenal-pituitary mechanism proposed by Sayer is involved in the production of lymphocytolysis during stress.

Of added interest is the fact that after the specific antibody titer in these immunized animals is exhausted, injection of ACTH or adrenal cortical hormone causes a measurable titer to the same specific antibody to reappear.

Forsham et al. have recently attempted to increase the titer of pre-existing antibodies in human subjects by administering ACTH but they were unable to demonstrate any such increase.

Chronic Stress

Studies on the effects of chronic stress have been less revealing and much more difficult to interpret than those on acute stress. As an example of certain easily detected changes, we noted in 1941 that both the blood sugar and liver glycogen levels were decreased in rabbits exposed for 35 days to a barometric pressure of 379 mm.Hg and even more strikingly diminished when the anoxia was more severe (382 mm. Hg). These decreases occurred despite the fact that autopsies on the rabbits revealed hypertrophy of the adrenal glands and atrophy of the thymus. It would appear from these results that in chronic stress, either the processes involved in building glycogen stores which are stimulated in acute stress by increased amounts of adrenal cortical hormone now become refractory to the hormone; or the adrenal cortices are secreting less hormone despite their increased size (exhaustion). The adrenal changes which we noted verified those produced in similar experiments by Armstrong and Heim. The striking decreases in the size of the thymus glands, however, were surprising at the time (1941) but not out of keeping with the old observations that there is a reciprocal relationship between the size of the thymus and the adrenal gland.

Of importance in any discussion of stress are the findings and theories of Selye. From evidence obtained by himself and others, largely in experimental animals, Selye has conceived the "adaptation syndrome," in which both acute and chronic phases of stress are considered. The material covered in the "Adaptation Syndrome" in its entirety is immense and beyond detailed consideration in this paper. Briefly, according to this theory, adaptation to all types of stress occurs in 3 stages:

1. The Alarm Reaction.
   a) shock.
   b) counter shock.
2. The Stage of Resistance.
3. The Stage of Exhaustion.

Details of one present concept of the alarm reaction have been covered in the discussion of the homeostatic theory of adjustment to acute stress in the preceding paragraphs.

In the stage of resistance, which follows the alarm reaction if the specific causative stress persists, most of the morphologic and humoral changes regress and a high degree of resistance to the causative stressful condition occurs. This resistance is acquired, however, at the expense of resistance to other stressful stimuli. Continued stress eventually exhausts the mechanism of resistance and the organism dies.

Clinical evidence of similar changes in man is lacking in completeness. Selye believes that certain disorders including rheumatic fever, periarteritis nodosa, hypertension, nephrosclerosis, nephritis and similar disorders should be classified as diseases of "adaptation." Perhaps somewhere in the causation of these disorders, chronic stress is of importance.

There seems to be less question as to the existence of an alarm reaction in man. The similarity of the response of normal humans to ACTH and stress and the lack of this response in patients with Addison's disease leave little doubt that the adrenal-pituitary mechanism is activated in humans under stress.

Recently, we were fortunate enough to be able to study a case of rheumatic fever on the wards of the Buffalo General Hospital. Attempts were made to procure evidence of an alarm reaction by determining serum uric acid levels and the renal excretion of uric acid.* The serum uric acid level

*Forsham et al. have shown that there is a consistently detectable rise in uric acid excretion in man following the injection of 11 oxysteroids and they are of the opinion that changes in uric acid excretion reflect the secretion of carbohydrate-regulating hormones by the adrenal cortices.

was found to be elevated on admission to the hospital two weeks after the onset of joint symptoms (Table I). The uric acid excretion was also found to be questionably elevated (Table I). It would appear from these figures that there was increased production of uric acid but the kidneys were unable to excrete this additional uric acid as rapidly as it was formed. For this reason, the serum level of uric acid increased. The increase of uric acid in the serum and urine is presumptive but not conclusive evidence that in this patient, the rheumatic fever caused an alarm reaction which resulted in adrenal cortical stimulation. This should not be accepted as evidence that rheumatic fever is a disease of adaptation, for could not fever and joint inflammation from any cause elicit an alarm reaction?

Summary

The role of the adrenal cortex in resistance to stress and strain has been reviewed. Certain experimental data indicating increased secretion of the adrenal cortical hormone in acute and chronic stress has been presented and discussed in terms of Sayers' homeostatic theory of the acute stress mechanism and in terms of Selye's "Adaptation Syndrome." In addition, studies made on a patient with acute rheumatic fever were discussed. Changes in uric acid metabolism compatible with those that might be seen in an alarm reaction were noted in this patient.

TABLE I

URIC ACID—PATIENT J.A.
RHEUMATIC FEVER

	Serum mg./100 ml.	Urine mg./hr.
Patient J.A.	7.0 (5.9–8.8)	37.2 (28.6–45.7)
Normal subjects (11)	5	25.2 (12.6–45.6)
Gouty arthritis (11)	8.2 (6.6–10.0)	30.4 (9.7–62.0)

PHYSIOLOGY OF ADRENAL CORTEX*

Nathan B. Talbot, M.D. (From the Department of Pediatrics, Harvard Medical School, and the Children's Medical Service, Massachusetts General Hospital, Boston, Mass.): *Introduction.* The adrenal cortex is comprised of three approximately defined zones: The glomerulosa (outer), fasciculata (middle) and reticularis (inner layer). In broad terms, adrenal cortical hormones also can be separated into three chief types; namely, those which (a) influence the metabolism of certain electrolytes and water, (b) alter sugar, fat and protein metabolism and (c) prompt protoplasmic anabolism and tend to masculinize. There is some evidence that the zona glomerulosa is the source of type (a), the fasciculata is the origin of type (b) and the reticularis is the producer of type (c) adrenal cortical hormones. Thus the adrenal cortex can almost be considered as three organs in one, each with a special function. In addition the adrenal cortex is known to produce small amounts of estrogenic or feminizing hormone as well as other types which have not as yet received extensive study.

The adrenal cortex bears an important relation to the anterior pituitary which secretes in all probability at least two adrenocorticotrophic hormones. In the absence of these trophic hormones the adrenal cortex involutes and becomes inactive. Under the stimulus of the trophic hormones the adrenal cortex enlarges and actively secretes hormones into the circulation.

Thorn et al. report a significant rise in the serum uric acid level as well as an increased uric acid excretion in a normal human subject after the injection of ACTH.

* The work reported here is based on studies supported by the Commonwealth Fund of New York.

For purposes of clarity, after a brief consideration of chemical aspects the three hormone types mentioned above will be discussed separately. It is to be emphasized that these discussions are incomplete, somewhat arbitrary and very much simplified. However, it is hoped that they cover most of the thoughts considered important today.

Chemistry of Hormones. Adrenal cortical hormones have a steroidal configuration like that of cholesterol from which they are probably derived. Over 30 different, but closely related, compounds have been isolated from animal adrenal glands. A detailed consideration of each of these would not contribute to the problems at hand. In general terms, however, it is helpful to recognize a few of their most important differential characteristics (Figure 1).

The hormone which is known to act almost exclusively on electrolyte and water metabolism is 11-desoxycorticosterone (I). This compound is commonly designated as desoxycorticosterone or desoxycorticosterone acetate (DOCA), the desoxy referring to the fact that there is no oxygen at carbon number 11. DOCA is the material available for clinical use, not the substance produced endogenously. The presence of an oxygen at position 11 greatly modifies the physiologic action

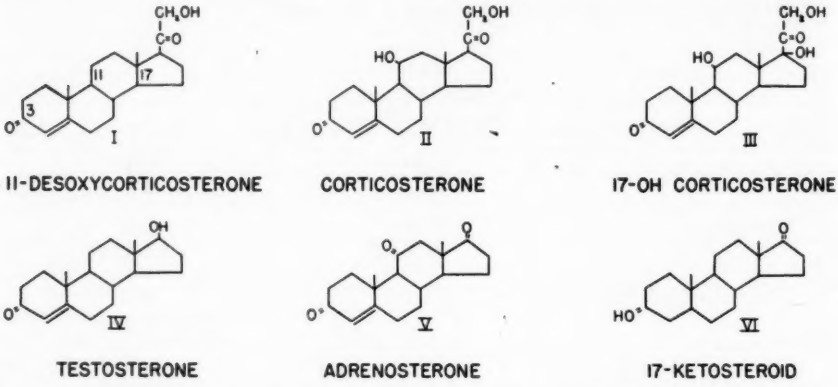

FIG. 1. Chemical Configuration of Representative Adrenal Cortical and Related Steroids.

of an adrenal steroid hormone. When the 11-oxygen is present (II) the steroid hormone loses a portion of its influence on electrolyte metabolism and acquires an influence on carbohydrate and fat metabolism. If in addition to an oxygen on carbon 11, a steroid also contains an hydroxyl group on carbon 17 (III), it has a more potent effect on carbohydrate and fat metabolism and only a nearly negligible effect on electrolyte and water metabolism. It now appears that certain of these steroids may partially cancel out the physiologic effects of others. Thus type III steroids may inhibit the action of type I steroid on sodium metabolism. As a consequence it may appear that in certain respects type III steroids have an action on water and electrolyte metabolism opposite to that of type I.

In contrast to the foregoing, steroids with a predominantly androgenic and nitrogen anabolic action are thought to have no oxygen on carbon 11 and no 2-carbon side chain on carbon 17, but to have an hydroxyl (IV) or ketone (V) group on carbon 17. It is this type of steroid which is metabolized and excreted in the urine as neutral 17-ketosteroids (VI).

Chemical assay procedures for clinical use have been developed for measurement of certain of these steroid hormones after they have been extracted from such biologic fluids as urine and blood. These procedures are reasonably specific with respect to hormone type, but do not distinguish between individual members of a given type. For example, steroids, such as compounds I, II, and III which have a 2-carbon sugar-like side chain, are reducing agents which can be assayed with the aid of suitably modified blood sugar procedures. Compounds IV, V and VI do not give this reaction. However, 17-ketosteroids (V, VI) react with certain chromogenic reagents (m-dinitrobenzene; antimony trichloride) to give intensely colored products which can be measured spectrophotometrically.

Electrolyte and Water Hormone ("Na-K" Hormone) 11-desoxycorticosterone is the best known example of this type of hormone. Whether this particular steroid is the natural regulator of electrolyte metabolism in the human is not known. In spite of this, it appears safe to say that the human adrenal cortex secretes steroids with a very similar type of action.

The electrolyte and water hormone acts primarily upon the tubules of the kidney, determining within certain limits how much sodium and potassium they can reabsorb from the glomerular filtrate as it flows through their lumina. It is because of this primary action that this hormone type has for purposes of abbreviation been labelled the "Na-K" hormone.

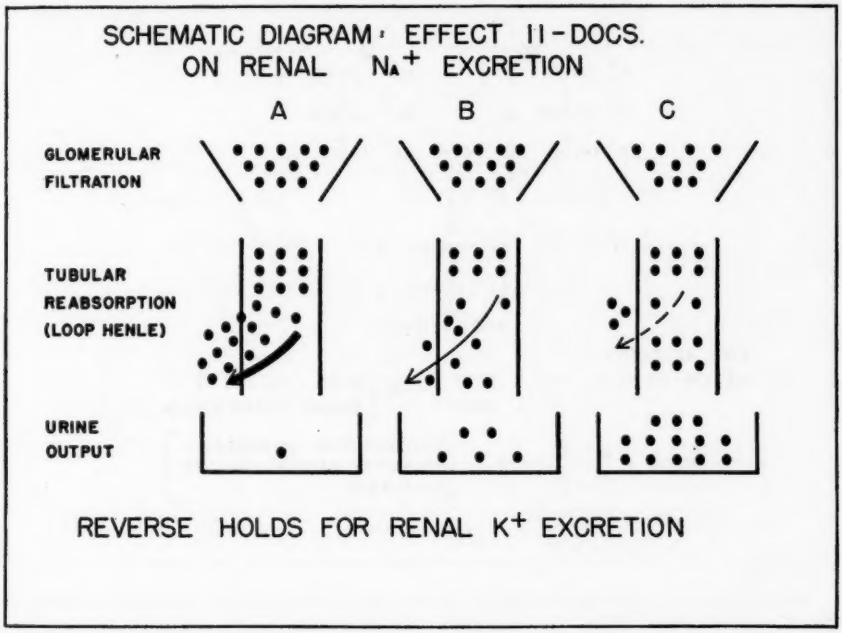

FIG. 2. Diagrammatic Representation of Effect of 11-Desoxycorticosterone on Renal Sodium and Potassium Excretion. Effect is on tubular reabsorption increases, urinary excretion relative to serum concentration (glomerular filtrate amount) decreases. In section A, concentration of 11-desoxycorticosterone is more than in B; in B it is more than in C.

The precise manner in which the "Na-K" hormone determines tubular sodium and potassium reabsorption is not clearly evident. That is, it is not certain that the "Na-K" hormone acts primarily on sodium and secondarily on potassium reabsorption versus primarily on potassium and secondarily on sodium, etc. Just what the relation is between these phenomena and tubular chloride reabsorption also is not understood in detail. However, certain broad relations are discernible from available evidence.

When the concentration of "Na-K" hormone increases, there tends to be an increase in renal tubular sodium reabsorption and a decrease in renal tubular potassium reabsorption (Figure 2). These alterations in tubular activity result in changes in the rates of excretion of sodium and potassium relative to their respective concentrations in the blood serum: sodium excretion is decreased, potassium excretion is increased. Opposite changes take place when the concentration of "Na-K" hormone falls.

When an excess of "Na-K" hormone results in a positive sodium and a negative potassium balance, the course of events outlined in Figure 3 takes place. It can be seen that with potassium loss,

there is a tendency to hypokalemia (serum potassium ↓) and also to intracellular potassium depletion. With sodium retention, there also is an overexpansion of extracellular water volume with edema, hypertension, etc. Further it is noted that sodium tends to replace or displace intracellular potassium. This exchange of sodium for potassium within the cells can be of considerable magni-

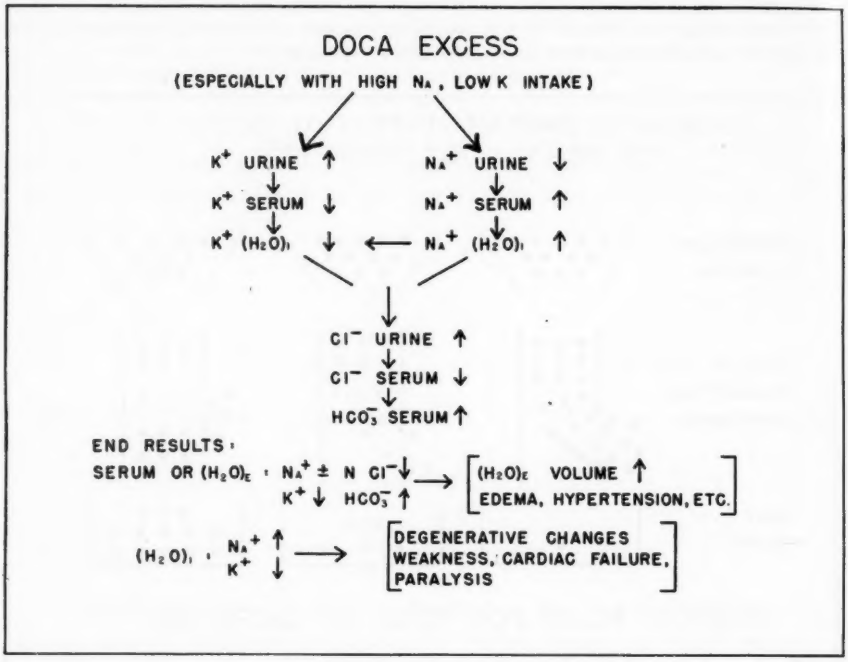

FIG. 3. Effects of 11-Desoxycorticosterone Excess on Body Economy Under Conditions of Ordinary Na, Cl and K Intake. Effects on extracellular and intracellular water composition, volume, etc., are augmented by increasing Na and decreasing K intake and are minimized by giving low Na, high K regime (see text).

tude. Normally intracellular water contains about 8 mEq/l. of sodium and about 150 mEq/l. of potassium. Under conditions of abnormal sodium retention, intracellular sodium may rise to levels as high as 50 mEq/l. and potassium may fall to levels of 100 mEq/l. or thereabouts. When such changes in intracellular electrolyte pattern occur, there is muscular weakness or paralysis. Apparently as a consequence of these chemical changes striking morphologic abnormalities in skeletal and cardiac musculature also become evident. The latter are reminiscent of but not identical with those seen in rheumatic carditis.

When sodium enters the cells and replaces potassium therein, extracellular-intracellular ionic equilibrium is maintained by depressing the extracellular chloride concentration. This hypochloremia may be the result of an increase in renal chloride or gastro-intestinal chloride excretion or both. To compensate for the hypochloremia there is an increase in serum bicarbonate concentration. The final picture of normo- to slight hypernatremia, hypokalemia, hypochloremia and increased serum bicarbonate is thought to be nearly diagnostic of the intracellular disturbances just described.

Finally, it is to be noted that the phenomena described above are not due to "Na-K" hormone excess per se. Rather they are due to excess sodium retention plus excess potassium loss. This combination can be produced in the absence of "Na-K" hormone excess by giving a high sodium,

zero potassium intake. Contrariwise, a very low sodium, high potassium regime essentially prevents an excess of "Na-K" hormone from causing sodium retention, potassium depletion and the sequelae described above.

To consider the opposite situation, a deficiency of "Na-K" hormone results in the abnormalities indicated in Figure 4. These are by and large the reverse of those outlined for "Na-K" hormone excess. Potassium is retained with resultant tendency to hyperkalemia. Hyperkalemia causes somatic and cardiac muscle weakness. The latter can be fatal to the subject. It is likely that potassium also accumulates within cell water. It has been claimed that this results in intracellular edema. Sodium and chloride, on the other hand, are lost from the body in abnormal amounts. As a result, extracellular fluid volume is apt to shrink with consequent extracellular dehydration, anhydremia, hypo-

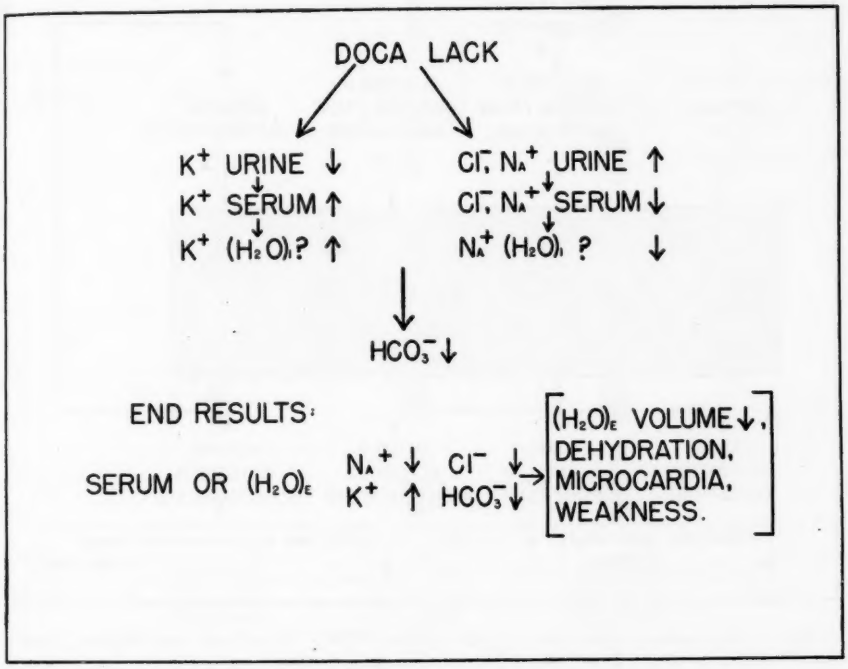

FIG. 4. Effect of 11-Desoxycorticosterone Lack on Body Economy Under Conditions of Ordinary Na, Cl and K Intake (see text).

tension, microcardia, etc. Hyponatremia and hypochloremia also are apt to develop. Moreover, because of circulatory failure renal function becomes impaired. This can result in the pathologic retention of such other blood constituents as nonprotein nitrogen and inorganic phosphorus.

As was the case for "Na-K" hormone excess, "Na-K" hormone deficiency must be viewed with relation to total body balances of sodium, chloride and potassium. A low sodium and chloride, high potassium intake aggravates the effects of "Na-K" hormone lack. The opposite type of regime ameliorates and even can eliminate most of the signs of "Na-K" hormone deficiency.

To summarize, the "Na-K" hormone has an important influence upon the rates at which the kidneys eliminate sodium, potassium and chloride from the body. Incidentally, it appears that this hormone acts similarly on the electrolyte excretion by sweat glands. Whether secondary changes in body water and electrolyte composition develop is dependent upon water, sodium, potassium and to a certain extent chloride intake values. This introduces a comment on homeostasis. It is of great import to the organism as a whole to produce amounts of "Na-K" hormone which are in keeping

with its homeostatic or physiologic needs. There are preliminary observations which suggest that in normal individuals spontaneous fluctuations in "Na-K" hormone occur when the intake of sodium or potassium is altered markedly. Future studies along these lines should prove extremely interesting and of considerable clinical importance.

The Sugar-Fat-Nitrogen Metabolism ("S-F-N") Hormone; The 11-17-Oxycorticosteroids ("11-17-OCS"). This hormone type exerts a number of effects which can be demonstrated experimentally and at times clinically by appropriate measurements. Though it is probable that all these effects are intimately related, it is convenient to consider them under three main headings: carbohydrate, fat and nitrogen. In addition there are certain miscellaneous actions which deserve brief mention.

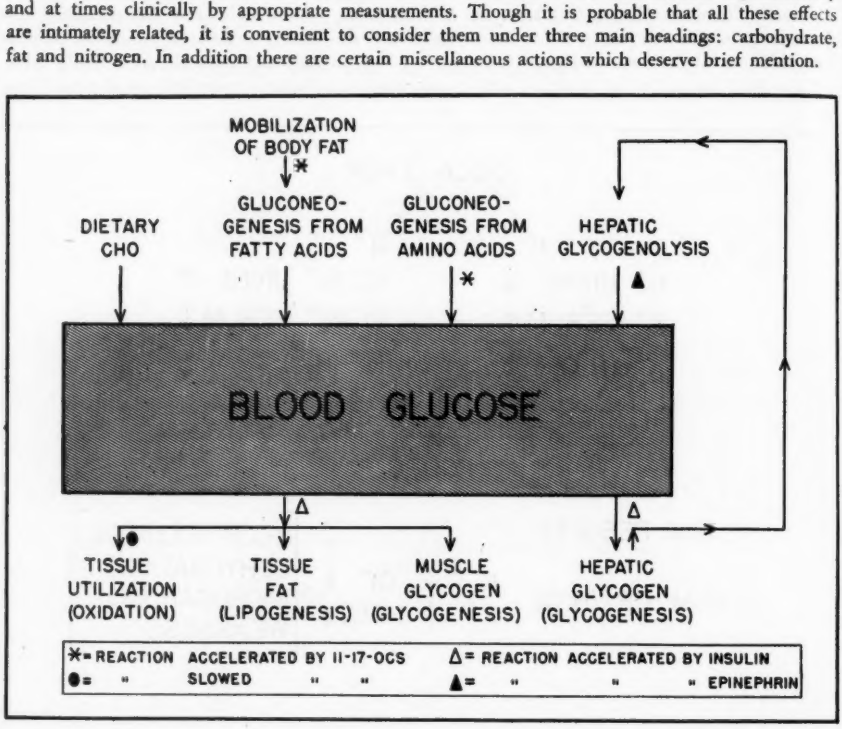

FIG. 5. Diagrammatic Illustration of Certain Factors Which Act to Raise Blood Glucose (upper set of arrows) or Which Lower Blood Glucose Concentration (lower set of arrows). Some of other factors which modify rates of certain of these reactions are shown also.

Effects on Carbohydrate Metabolism. Carbohydrate metabolism is a complex phenomenon and the literature contains a vast amount of information concerning it. A considerable number of the ideas recorded are currently the subject of vigorous debate. Accordingly it is at present difficult to present more than an oversimplified picture of what is thought to be approximately true.

Figure 5 may aid in these considerations. Here are indicated potential sources of blood glucose and potential routes or mechanisms by which glucose may be withdrawn from the circulation. It is seen that dietary carbohydrate is not the only source of circulating glucose. On the contrary, glucose may be formed (gluconeogenesis) within the body from amino acids and from fat. In addition, limited amounts of glucose can be released into the blood stream by lysis of hepatic glycogen stores. The foregoing are on the credit side of the blood glucose balance sheet. On the debit side are tissue utilization or oxidation, tissue fat deposition, muscle glycogen formation and hepatic glycogen deposition.

Next it will be noted that the "S-F-N" hormone or "11-17-OCS" are thought to accelerate certain of these reactions and to slow others. Thus gluconeogenesis from protein and mobilization of body

depot fat proceed with increasing rapidity as the concentration of "11-17-OCS" increases. Concomitantly there is a decrease in the rate at which the peripheral tissues utilize circulating glucose. Current information suggests that the "11-17-OCS" have a quantitatively much more pronounced effect upon the rates of tissue carbohydrate utilization and depot fat mobilization than upon the rate of gluconeogenesis from protein (amino acids).

The diagram of Figure 5 illustrates an additional point, namely, that there are other factors which act to modify the rates at which glucose is entering and leaving the blood stream. Only two factors are indicated though others are known to exist. One of these, insulin, increases the rate

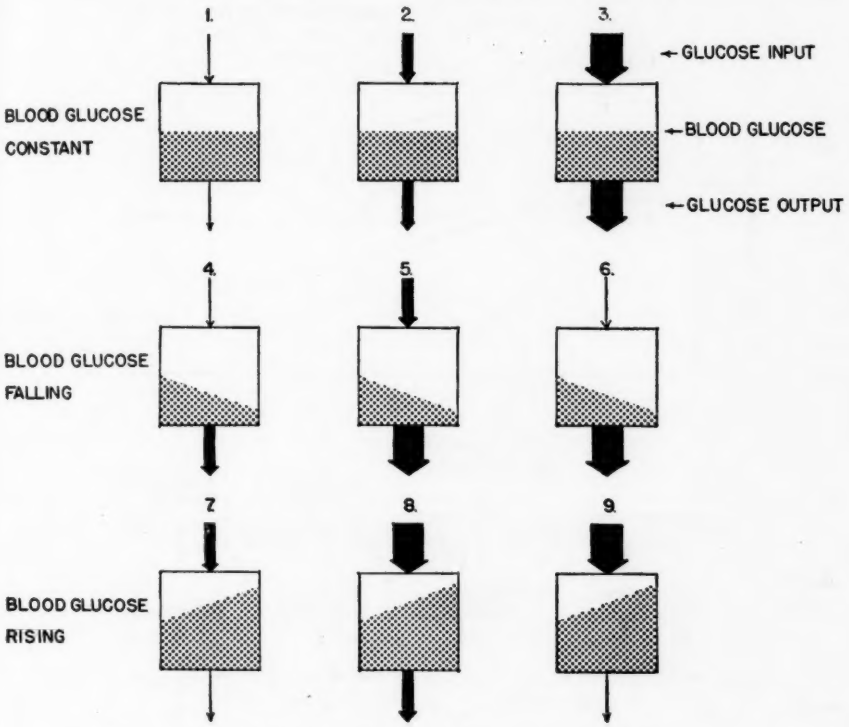

FIG. 6. Possible Relations Between Blood Glucose Input and Output and Blood Glucose Concentration.

at which circulating glucose is utilized for such purposes as oxidation, lipogenesis and glycogenesis. This effect is mediated at least in part by acceleration of glucose phosphorylation, an essential first step in the utilization of glucose for these purposes. The other, epinephrin, tends among other things to accelerate the rate at which hepatic glycogen is transformed into blood glucose. It is hoped that inclusion of these factors may clarify later discussions of various carbohydrate tolerance tests.

The foregoing serves as a basis for considering the effects of "S-F-N" hormone deficiency upon blood sugar concentration values. In Figure 6 a number of possible relations between the rate of blood glucose intake or input, blood glucose concentration and blood glucose loss or output, respectively, are set forth. It is seen that when intake equals output (Conditions 1, 2, 3) blood glucose remains constant. This relation holds regardless of the rates of intake and output provided they are equal. When, however, intake is less than output (Conditions 4, 5, 6) the concentration of

glucose in the blood must fall. Contrariwise, the concentration of glucose in the blood must rise when blood glucose intake exceeds output (Conditions 7, 8, 9). Again, it is the relation between the two variables, glucose addition and glucose withdrawal from blood, rather than the absolute values for the variables which determines changes in blood sugar concentration.

As suggested by Figure 5, an excess of "S-F-N" hormone results in a tendency to hyperglycemia, probably chiefly by inhibiting peripheral tissue glucose utilization (Condition 7). "S-F-N" hormone lack has the expected opposite effect of producing a tendency to hypoglycemia. It seems likely

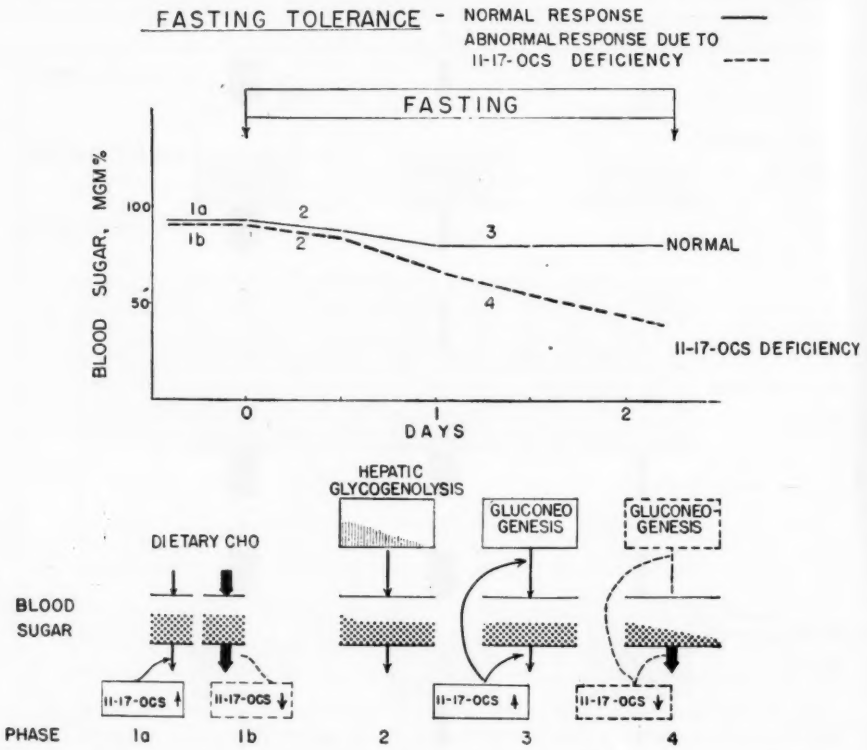

FIG. 7. Diagrammatic Representation of Changes Occurring When Normal and 11-17-OCS Deficient Individual is Fasted. Blood sugar values are indicated against time in upper section of figure. Numbers shown adjacent to blood sugar curves refer to smaller diagrams at lower margin of chart. Diagrams attempt to portray manner in which various mechanisms operate and time during which they are most important.

that this tendency is due to an absolute increase in peripheral glucose utilization (Condition 5) or to a combination of this and failure of gluconeogenesis from protein (Condition 6).

These phenomena can be studied in a crude manner by various carbohydrate tolerance tests in which changes in blood glucose concentration are measured. The two extremes, "S-F-N" hormone lack (hypoadrenocorticism) and "S-F-N" hormone excess (hyperadrenocorticism of the Cushing's syndrome type) will be reviewed.

When "S-F-N" hormone is absent, the individual gets along quite satisfactorily so long as his carbohydrate intake is adequate. This situation is roughly approximated by Condition 3 of Figure 6 where it is suggested that an increase in carbohydrate ingestion has compensated for an increase

in glucose utilization and a decrease in gluconeogenesis from protein. If, however, the carbohydrate intake is reduced or eliminated as by fasting, Conditions 5 or 6 supervene and hypoglycemia develops within a day or so (Figure 7). In Figure 7, in the normal individual, phase 1 indicates a control state of equilibrium with normal blood sugar. During the early phases of the fast, blood sugar is maintained by hepatic glycogenolysis (phase 2). Later, when hepatic glycogen is largely gone, gluconeogenesis from protein (and possibly from fat also) prevents hypogly-

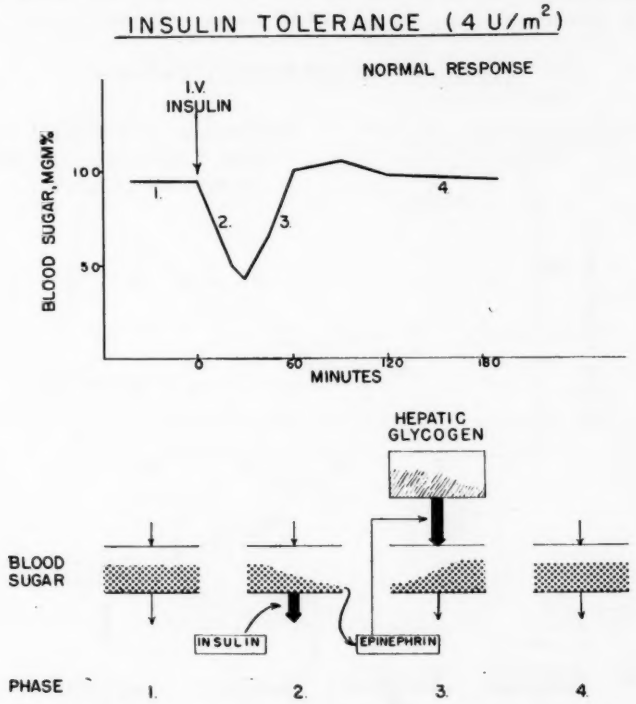

FIG. 8. Diagrammatic Representation of Intravenous Insulin Tolerance Test in Normal Person. Construction of diagram is same as figure 7.

cemia (phase 3). By contrast, the 11-17-OCS deficient subject has lost his ability to form new sugar and at the same time is utilizing or oxidizing sugar at an increased rate (phase 4). This results in hypoglycemia.

Another method which has been recommended for the demonstration of this hypoglycemic tendency is the insulin tolerance test. Reference to Figures 8 and 9 will reveal that insulin increases the relative rate at which glucose leaves the blood stream. Thus a single intravenous dose of insulin characteristically prompts an acute fall in blood sugar concentration. Normally, this period of relative hypoglycemia is transient because hypoglycemia prompts the release of epinephrin by the adrenal medulla. The epinephrin in turn prompts hepatic glycogenolysis which serves to elevate blood sugar concentrations (Figure 8). If the adrenal medulla is intact and glycogen stores in the liver are adequate, patients with hypoadrenocorticism also may respond in an essentially normal manner when subjected to the intravenous insulin tolerance test. On the other hand, if the adrenal glands including the medulla are totally destroyed and/or if hepatic stores of glycogen are already depleted, insulin will cause hypoglycemia which cannot be corrected spontaneously (Figure 9). This state sometimes is called hypoglycemia unresponsiveness.

A closely similar picture can be evoked in patients with panhypoadrenalism by administering

glucose intravenously. The hyperglycemia thereby induced is thought to stimulate the production of endogenous insulin (Figure 10). When the intravenous glucose infusion is stopped this endogenous insulin prompts the train of events just outlined for parenterally administered insulin. However, time relations are spread out. Consequently, hypoadrenocortical patients should be watched for evidences of hypoglycemia 3 to 6 hours following cessation of intravenous glucose therapy whereas they are apt to become hypoglycemic within 20 to 30 minutes after insulin has been given intravenously.

When, in contrast to the foregoing, the "S-F-N" hormone is present in excess more or less

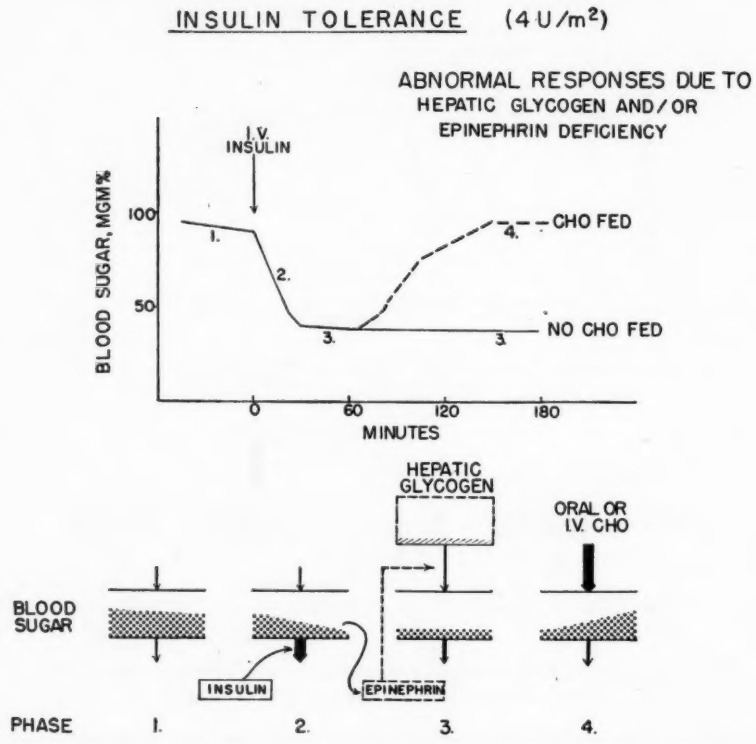

FIG. 9. Diagrammatic Representation of Intravenous Insulin Tolerance Test in Subject Suffering from Hepatic Glycogen Depletion or Adrenal Medullary Deficiency. Note that blood sugar remains low (phase 3) unless exogenous carbohydrate is given (phase 4) (see also figure 7).

opposite phenomena are observed. Fasting usually is without abnormal consequence, presumably because increased gluconeogenesis from protein is not quantitatively sufficient to result in fasting hyperglycemia. Moreover, any tendency to hyperglycemia can be partially counteracted by an increased endogenous production of insulin. The resultant metabolic picture probably corresponds roughly to Conditions 1 or 2, Figure 5.

The intravenous glucose tolerance test has been found in patints with hyperadrenocorticism of the Cushing's syndrome type to result in a diabetic type of blood glucose curve (Figure 11). It is presumed that the blood sugar falls abnormally slowly because excess "S-F-N" hormone inhibits utilization of glucose by body tissues perhaps in part by antagonizing the action of insulin. At any rate is seems that the quantity of the insulin which is produced endogenously in response to

hyperglycemia is insufficient to overcome this adrenal hormone action immediately, an idea supported by the fact that when insulin is administered with the glucose there still results a diabetic type of blood sugar curve (insulin resistant diabetes).

Effects on Fat Metabolism. This already has been mentioned in the preceding section. In the absence of the "S-F-N" hormone, the organism loses its normal capacity to mobilize depot fat. Consequently, even under conditions of fasting there is little tendency to ketone body formation or ketonuria. By contrast, an excess of "S-F-N" hormone accelerates body fat mobilization and produces

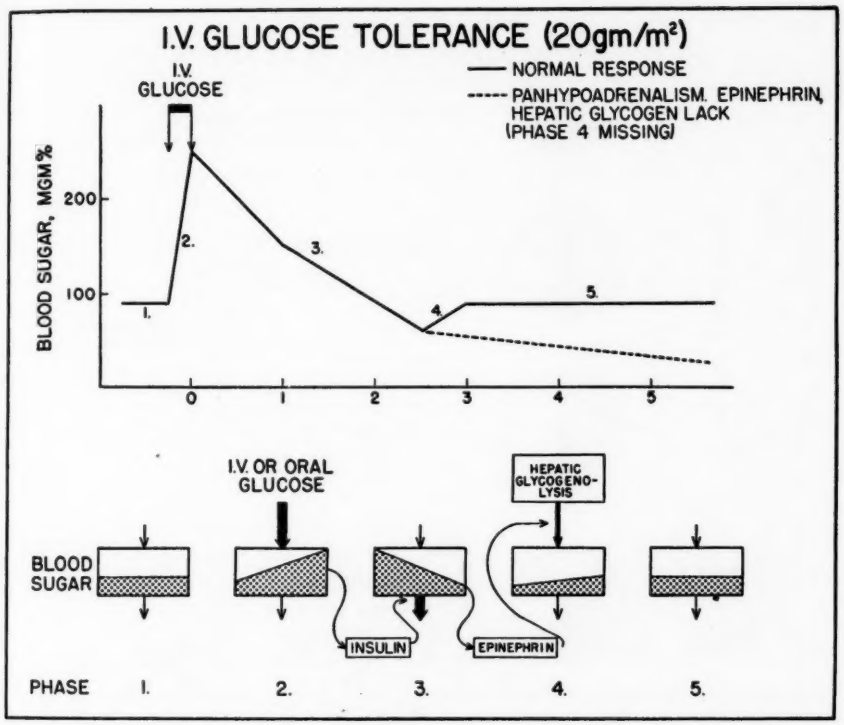

FIG. 10. Diagrammatic Representation of Intravenous Glucose Tolerance Tests in Normal Person and in Patient with Panhypoadrenalism.

a tendency to ketosis. It is not known whether this type of adrenal hormone per se modifies the rate at which fatty acids and ketone bodies are utilized.

Effect on Nitrogen Metabolism. This effect also was mentioned in the preceding section on carbohydrate metabolism. To recapitulate, the "S-F-N" hormone is one of the factors which accelerates amino acid breakdown (nitrogen catabolism) with resultant gluconeogenesis. Other hormonal agents which influence this phenomenon (though in the opposite way) are the pituitary growth or somatotrophic hormone and the testicular and adrenal cortical androgens. These are thought to inhibit nitrogen catabolism or promote nitrogen anabolism. Caloric balance (i.e., ratio of caloric intake to caloric output) also bears a relation to nitrogen metabolism. A positive caloric balance favors nitrogen anabolism, a negative caloric balance, nitrogen catabolism.

Viewed with relation to the foregoing incomplete list of other factors which influence nitrogen metabolism, the "S-F-N" appears not to be quantitatively very important. Qualitatively, however, the "S-F-N" hormone produces interesting changes in certain tissues. Especially the

lymphoid structures including the thymus and the circulating eosinophiles undergo involution or lysis when the concentration of "S-F-N" hormone is increased. This is reflected clinically by a shrinkage in the size of the thymus (so-called acute accidental involution) and by the development of eosinophilopenia and lymphopenia. This tissue catabolism also is reflected by an increased rate of urinary uric acid excretion. The physiologic implications of these phenomena are not clear as yet.

Summary Comments. The over-all effect of the "S-F-N" hormone on sugar, fat and nitrogen metabolism is illustrated by Figure 12. Here it can be seen that in "S-F-N" hormone lack carbo-

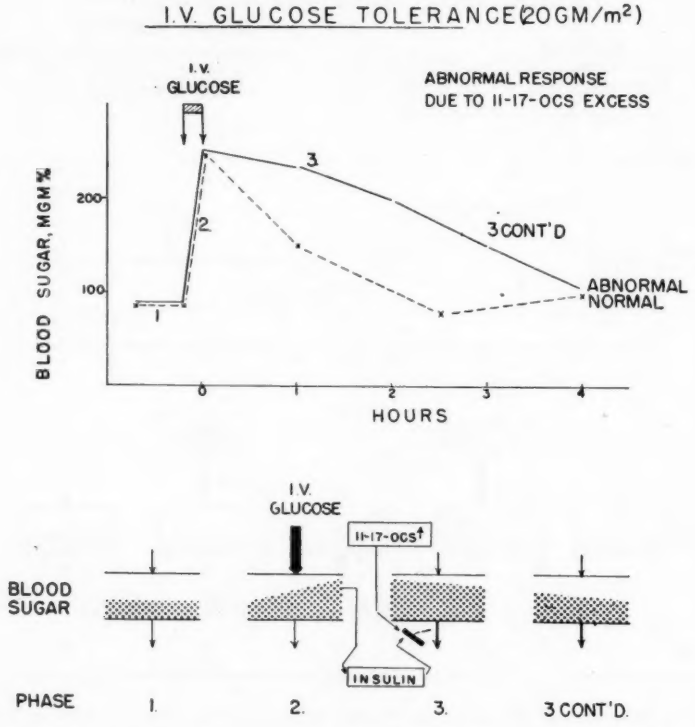

FIG. 11. Diagrammatic Representation of Intravenous Glucose Tolerance Test in Patient with Excess 11-17-OCS (see also Fig. 7).

hydrate is the major source of calories. When this hormone deficiency is corrected or an excess of the hormone is given, fat becomes a much larger and carbohydrate a much smaller source of calories. Protein metabolism is influenced to a much smaller degree than carbohydrate and fat metabolism. However, protein occupies a slightly greater portion of the total metabolic mixture when "S-F-N" hormone is present than when it is lacking. Incidentally, it can be noted in Figure 12 that desoxycorticosterone acetate and adrenal cortical extract did not inhibit carbohydrate or augment fat utilization.

Finally it can be stated that the rate of production of the "S-F-N" hormone as estimated by measurements of the urinary 11-17-OCS output is per square meter of body surface per day the same for individuals of all ages (Figure 13). However, the output of these substances increases markedly when persons are exposed to the stress of acute illness, operation, trauma or the like.

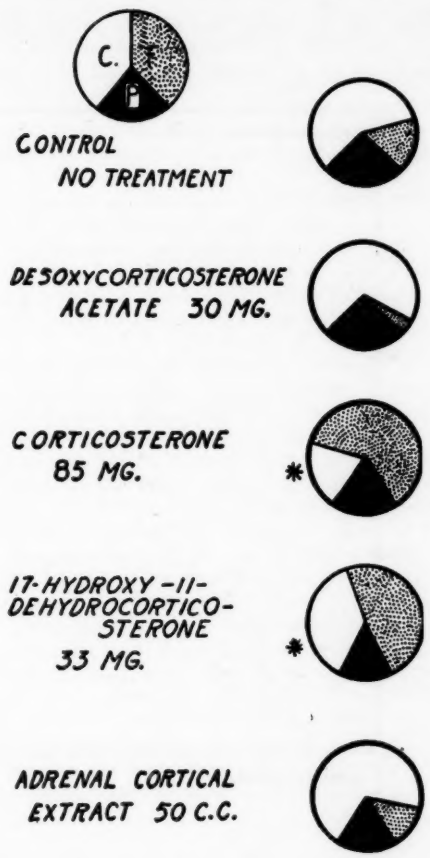

FIG. 12.* Effect of Adrenal Cortical "S-F-N" Hormone on Relative Proportions of Carbohydrate, Fat and Protein Being Oxidized to Provide Organism with Energy. Configuration of various circles of diagram indicate approximate composition of metabolic mixture from which calories were derived in patient with hypoadrenocorticism. White area stands for carbohydrate; speckled for fat; black for protein.

* From Thorn, G. W., Koepf, G. F., Lewis, R. A., and Olsen, E. F., Carbohydrate metabolism in Addison's disease, J. Clin. Investigation 19:813, 1940.

These changes in production rate are not due to primary changes in the adrenal cortex. On the contrary, they are brought about by corresponding changes in the concentration of a specific adrenocorticotrophic hormone produced by the anterior pituitary gland.

Androgenic or Protein Anabolic ("N") Hormone (Urinary 17-Ketosteroid Precursors). It has been admitted that the exact composition of this third type of adrenal hormone is not known. However, it appears to have properties reminiscent of the testicular hormone, testosterone, though it appears to be less active per unit weight and to have slightly different biologic properties. It has been postulated that the adrenal androgens are not produced as such by the adrenal cortex, but are merely metabolites of the 11-OCS or 11-17-OCS. The evidence presented in favor of this thesis is not as yet convincing.

In contrast to the "Na-K" and the "S-F-N" hormones the adrenal androgens or "N" hormone must be considered with relation to the age of the subject. As indicated by urinary 17-ketosteroid* measurements, adrenal androgens are not normally produced in appreciable quantities until about

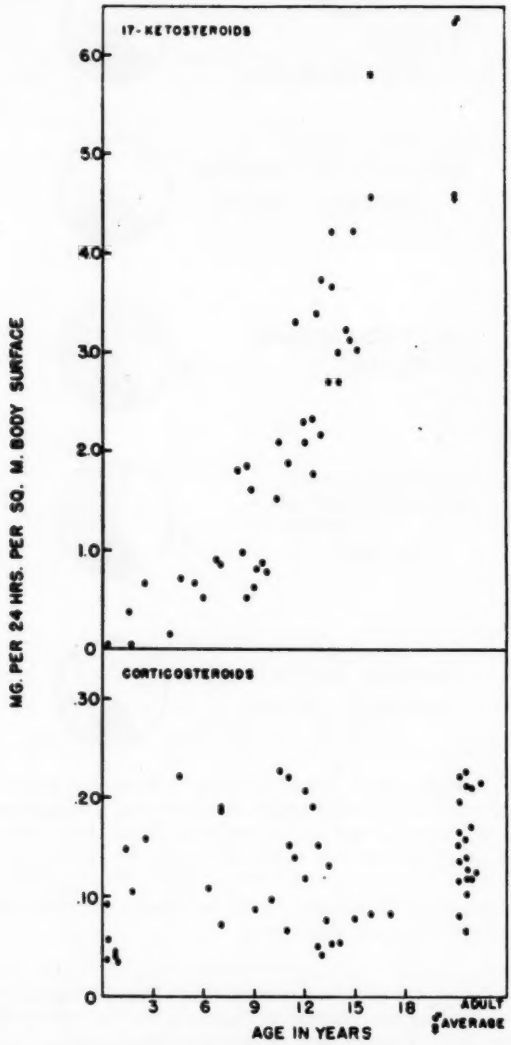

FIG. 13. Urinary 11-17-Oxycorticosteroid and 17-Ketosteroid Output by Normal Individuals of Various Ages. Results are expressed as mg./sq.m. of body surface/day.

* There is only one other source of urinary 17-ketosteroids, namely, the testis. While testicular androgens do contribute to the urinary 17-ketosteroid output of boys, they appear to do so only to a relatively small extent. Accordingly the urinary 17-ketosteroids may be considered entirely representative of adrenal androgen foundation in girls and nearly so also in boys.

the 8th year of life (Figure 13). Thereafter they are produced in steadily increasing quantities until adolescence is completed. The inflection point at about the 8th year may be called the "adrenarche."

In the adolescent and adult female, failure of production of adrenal androgens results in a failure to grow pubic and axillary hair and to develop adolescent acne. Other evidences of deficiency are difficult to demonstrate. In the male, absence of adrenal androgen is almost impossible to detect for the testicular androgens bring about all of the changes which might be ascribed to adrenal androgens.

On the other hand, excessive or precocious adrenal androgen production can lead to marked degrees of virilism in the female (including pseudohermaphroditic changes in the female fetus) or to pseudoisosexual precocity in the preadolescent male. In association with these changes, there is apt to be accelerated growth in stature and musculature and an acceleration in skeletal maturation which leads to early cessation of growth and hence small adult stature. The accelerated growth and muscular hypertrophy reflect an increased rate of protein anabolism. Hence the term, nitrogen or "N" hormone.

As for the "S-F-N" hormone, the "N" hormone is produced by the adrenal cortex under the influence of a specific adrenocorticotrophic hormone elaborated by the anterior pituitary. Also as described for the "S-F-N" hormone, adrenal "N" hormone varies about the normal for age when persons suffer stress of appreciable degree. During the initial phase of the stress there may be an increase in 17-ketosteroid output. However, in contrast to the "S-F-N" hormone, "N" hormone secretion as measured by the 17-ketosteroid output is apt to decrease when stress is prolonged. The clinical significance of these presumably homeostatic phenomena remains to be clarified.

In conclusion, the adrenal cortex has been described as an organ which produces in variable amounts at least three important types of hormone. By their respective actions on electrolyte and water metabolism, sugar, fat and protein metabolism and on masculine sex structures and bones these adrenal cortical hormones are able to exert a profound influence upon every organ in the body. As such, the adrenal cortices appear worthy of serious attention. The likelihood that such attention may yield clinically useful information seems augmented by the fact that disease conditions of all sorts evoke marked physiologic changes in adrenal secretory activity. It seems a reasonable premise that such changes usually have a homeostatic or beneficially corrective influence upon body economy. On the other hand, it is quite possible that there are circumstances where such changes in adrenal activity may work against the best interests of the organism. Stated in other words, physiologic variations in adrenal activity may ultimately prove to be clinically more important, though no more interesting than the pathologic variations about to be described.

HYPERADRENOCORTICISM

Classification of Type

Lawson Wilkins, M.D. (From the Department of Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital, Baltimore, Md.): The previous speaker has discussed the three principal groups of steroids of the adrenal cortex which act respectively as electrolyte-controlling, carbohydrate-regulating and androgenic hormones. It is not surprising that neoplastic or hyperplastic disorders of the gland may give rise to a wide variety of symptoms attributable to excess of one or of a number of these different hormones. However, as shown in Table I, cases of hyperadrenocorticism may be divided on the basis of their predominating metabolic manifestations into two main groups, the adrenogenital syndrome and Cushing's syndrome. Children with the adrenogenital syndrome show not only excessive masculinization but also rapid growth in height, marked muscular development and accelerated epiphysial ossification. These are evidences of increased protein anabolism due to excessive production of androgen. Clinical evidences of hypersecretion of the carbohydrate-regulating and electrolyte-controlling hormones are lacking, and in some cases of congenital adrenal hyperplasia there are Addison-like symptoms which will be discussed later. Children with Cushing's syndrome present a marked contrast in the metabolic picture to those with the adrenogenital syndrome. They are somewhat stunted in growth and have poor musculature, osteoporosis and marked obesity. Frequently they

have a diabetic type of sugar curve. These signs indicate that there is deficient protein anabolism in spite of the fact that there is also increased secretion of androgen as indicated by the occurrence of hirsutism and increased output of urinary 17-ketosteroids. Accordingly, in Cushing's syndrome one might surmise that both the gluconeogenetic and androgenic hormones are increased but that there is a preponderance of the former, causing amino acids to be utilized for the formation of carbohydrate rather than the building of protein tissues. In some cases of Cushing's syndrome there are evidences also of increased elaboration of salt-retaining hormones. A few girls with Cushing's

TABLE I

CLASSIFICATION OF HYPERADRENOCORTICISM

	Etiology	Evidences of Hormonal Dysfunction			
		Electrolyte Cortins	Glyco-genetic Cortins	Androgen	Estrogen
Adrenogenital Syndromes					
A. Congenital					
Female—pseudohermaphroditism	Hyperplasia of adrenal	N or −	N?	+++	
Male—macrogenitosomia precox					
B. Postnatal					
Female—virilization	Tumor or hyperplasia of adrenal	N	N	+++	
Male—precocity or excess virility					
Cushing's Syndrome	Hypothalamic lesion Basophil adenoma of pituitary Adrenal tumor or hyperplasia	+	+++	+	N or +
Feminizing Tumor—Gynecomastia	Tumor of adrenal	N	N	N or +	+++

syndrome have shown precocious breast development and menstruation, suggesting that the adrenals might be the source of estrogens.

The gynecomastia which occurs in rare cases of feminizing tumor of the adrenal may be due to estrogens, although at times the principal steroids found in the urine of these patients are pathologic types of androgen.

The Adrenogenital Syndrome

Manifestations According to Sex and Time of Onset. The manifestations of the excessive production of adrenal androgen depend upon the sex of the patient and upon whether the hormonal dysfunction begins in early embryonic life or after the intrauterine differentiation of the sex organs is complete. The effects upon sexual development may be classified as shown in Table II.

Congenital adrenal hyperplasia in females is the most common adrenal disorder encountered in childhood. The diagnosis depends upon the findings of (1) characteristic embryologic abnormalities of sex differentiation and (2) evidences of excessive production of androgen from early infancy on.

Embryologic Abnormality of Sex Differentiation. The condition gives rise to an almost uniform type of female pseudohermaphroditism. The patients have ovaries. The Müllerian duct system undergoes normal female development to form Fallopian tubes, uterus and vagina while the Wolffian ducts disappear. However, as shown in Figure 1 the genital duct continues to open into the urethra

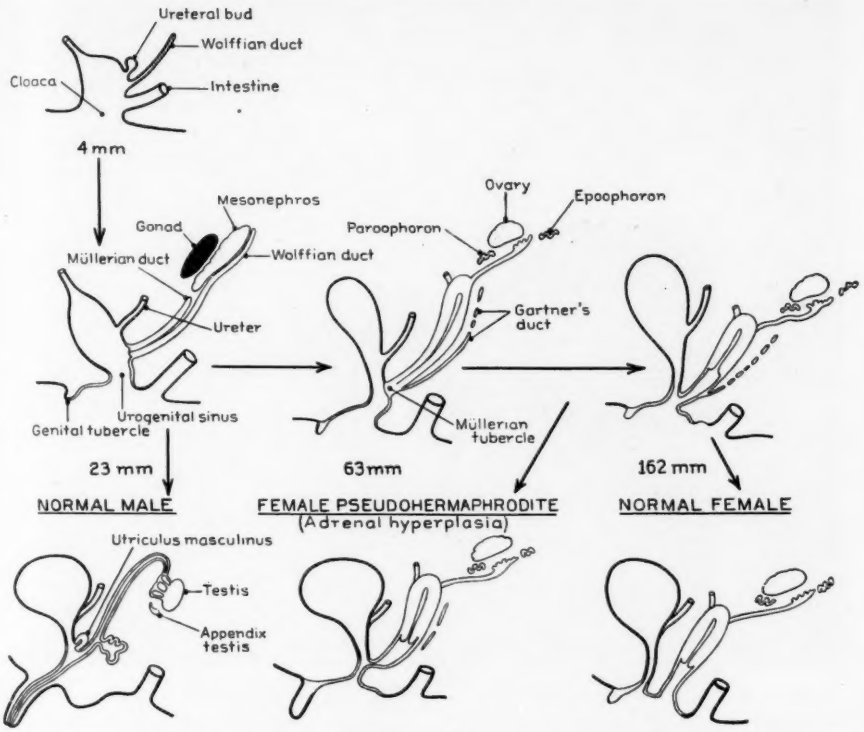

FIG. 1. Embryologic Development of the Urogenital Sinus. At 23 mm. stage embryo is ambisexual with both Müllerian and Wolffian ducts. By 63 mm. stage Müllerian duct shows complete development in female while Wolffian duct has disappeared. Vagina is joined to urogenital sinus by Müllerian tubercle which is not yet patent. After this vagina at first communicates with urogenital sinus but with growth of anterior vaginal wall separation of vagina and urethra is completed about stage of 162 mm. embryo. Virilizing effects of congenital adrenal hyperplasia are probably manifested between 63 mm. and 162 mm. stage (12 to 20 weeks).

forming a persistent urogenital sinus as in the male, whereas in normal females the urogenital sinus develops into a separate urethra and vagina which open into the vulva. This abnormality of sex differentiation suggests that the effects of androgen become manifest after the 11th or 12th week

TABLE II

MANIFESTATIONS OF ADRENOGENITAL SYNDROME ACCORDING TO SEX AND TIME OF ONSET

Onset of Disorder	Adrenal Lesion	Resulting Abnormality	
		Female	*Male*
A. Congenital	Hyperplasia	Pseudohermaphroditism	Macrogenitosomia precox
B. Postnatal	Tumor or hyperplasia	Virilization	Macrogenitosomia precox (before puberty) Excessive virility? (after puberty)

of fetal life when the differentiation of the genital ducts is complete, and before the 5th month when the normal urethral and vaginal relationships are attained.

At birth the clitoris is found to be hypertrophied, resembling a hypospadial penis and is bound ventrally by fibrous cords extending backward from the under surface (see Fig. 2). Between the labia minora there is a shallow, trough-like vulvar depression covered with mucous membrane. Into this opens the urogenital sinus usually with a small orifice resembling the meatus urethrae. If one examines with the urethroscope or makes a vaginogram after injecting lipiodal (see Fig. 3), it is usually possible to demonstrate the communication with the vagina. However, minor variations may

FIG. 2. External Genitalia of Pseudohermaphrodite with Congenital Adrenal Hyperplasia. Arrow points to single orifice of urogenital sinus.

be found in the anatomic relations of the urogenital sinus as shown in Fig. 4: (1) usually the orifice of the urogenital sinus is small and resembles the meatus urethrae; (2) at times the urogenital sinus opens through a larger funnel-like orifice resembling a small vagina rather than the urethra; (3) occasionally the communication between the vagina and urethra is not patent, although the relationships are otherwise the same; (4) in one case the vagina opened into the posterior portion of a penile urethra. It is possible that if congenital adrenal hyperplasia should begin after the 5th month of fetal life a separate vagina and urethra would be found. Actually, practically all the verified cases reported have shown some type of urogenital sinus.

Evidences of Secretion of Excessive Androgen. From birth on these infants continue to show evidences of increased secretion of androgen. Somatic growth, muscular development and epiphysial ossification become far advanced for the age of the patient. For example, by the 4th or 5th year the height age may be 8 years and the bone age 11 years. Frequently pubic hair appears by the age of 2 to 5 years, followed shortly by axillary hair. Acne develops early. Hypertrophy of the clitoris increases and there may be almost constant erections. The voice becomes deep. The excretion of

FIG. 3. Vaginogram (in Lateral Position). Pseudohermaphrodite with Urogenital Sinus. Catheter has been placed in bladder. Lipiodol, injected into urogenital sinus from syringe beside catheter, has entered and filled vagina.

17-ketosteroids is always increased in relation to the patient's age. During the first year the output may not exceed 2 to 3 mg. per day, although in some cases it is as high as 15 mg. per day. In later childhood the output usually rises to 15 to 40 mg. per day. The child's general appearance may be quite feminine in early childhood. However, at the age of adolescence, development of the breasts and menstruation fail to occur. Epiphysial fusions occur early. The patients often become short, stocky, muscular individuals with coarse dark hair on the thighs, legs, abdomen and face.

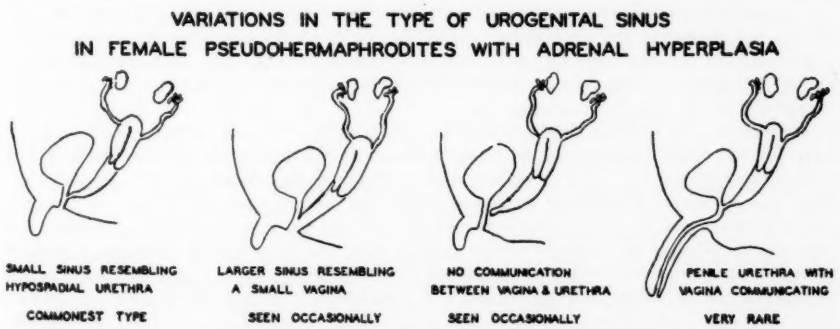
VARIATIONS IN THE TYPE OF UROGENITAL SINUS
IN FEMALE PSEUDOHERMAPHRODITES WITH ADRENAL HYPERPLASIA
SMALL SINUS RESEMBLING HYPOSPADIAL URETHRA
COMMONEST TYPE
LARGER SINUS RESEMBLING A SMALL VAGINA
SEEN OCCASIONALLY
NO COMMUNICATION BETWEEN VAGINA & URETHRA
SEEN OCCASIONALLY
PENILE URETHRA WITH VAGINA COMMUNICATING
VERY RARE

FIG. 4. Variations in Type of Urogenital Sinus.

Differentiation from "Genetic Intersexes." As shown in Table III the diagnosis of congenital adrenal hyperplasia and its differentiation from certain types of genetic intersexuality depend upon the finding in early childhood of these evidences of excessive androgen production which have been enumerated. There are various theories concerning the etiology of other types of intersexuality but one of the most likely is that there is an abnormal mosaic of male and female genetic components which govern differentiation. Various types of abnormalities occur in the differentiation of the sex organs, some of them resembling female pseudohermaphroditism of the adrenal type. For example, we have seen an individual with testes who had Fallopian tubes, uterus and a vagina opening into a urogenital sinus. However, unlike patients with congenital adrenal hyperplasia, genetic intersexes show no evidence of abnormal production of sex hormone during childhood and secondary sexual characteristics do not develop until about the usual age of puberty, when the pituitary assumes its gonadotropic activities.

Congenital Adrenal Hyperplasia in Males (Macrogenitosomia precox). *Familial incidence.* Congenital hyperplasia of the adrenal occurs in males as well as females but has been recognized less

TABLE III

DIFFERENTIATION OF TYPES OF HETEROSEXUAL DEVELOPMENT

	Abnormality of Embryonic Sex Differentiation	Evidence of Excessive Hormone			
		Excess Growth	Advanced Bone Age	Precocious Sexual Hair	17-K.S.
I. Hormonal Sex Reversal					
A. Embryonic					
Adrenal hyperplasia	Urogenital sinus	+++	+++	+++	++
B. Postnatal					
Adrenal tumor					+++
Adrenal hyperplasia	0	(depend on time of onset)			++
Arrhenoblastoma					±
Feminizing tumor of adrenal	0	0	0	0	(estrin)
II. Genetic Intersexes	Various abnormalities	0	0	0	Normal

frequently, probably because in many instances the patients have died in early infancy. The condition frequently occurs in siblings, the females showing pseudohermaphroditism and the males precocious development of secondary sex characteristics of a type which we call "macrogenitosomia precox" to distinguish it from other types of sexual precocity. In certain families as many as 2 to 5 children have had the disorder while other sibs have been normal, but we do not know of its occurrence in successive generations. On the other hand, genetic intersexuality seems to be hereditary. The cause of congenital adrenal hyperplasia is unknown; the parents have shown no evidence of endocrine dysfunction and the mothers have been well during pregnancy.

Differentiation from Other Types of Male Sexual Precocity. Although in some cases the penis is large at birth, frequently the child dies in early infancy of Addisonian-like symptoms, or if he survives he may reach 2 to 3 years of age before the genitalia attain sufficient size to attract attention. From then on sexual development progresses rapidly and the penis and prostate may attain adult size at an early age. Sexual hair and acne develop early and the voice becomes deep. Skeletal and muscular development are markedly accelerated as in girls with the condition. However, in spite of these evidences of excessive secretion of androgen the testes do not mature and in most cases remain of infantile size. As shown in Table IV this is of considerable importance in distinguishing adrenal hyperplasia from male sexual precocity due to hypothalamic lesions or caused by an early activity of the pituitary gland. In the latter conditions there is a premature activation of a normal pituitary-

gonadal mechanism, which causes the patient's testes to grow and mature and may bring about spermatogenesis. On the contrary, when excessive androgen is secreted by the adrenal the development of the patient's testes is inhibited (see Fig. 5). Occasionally, as in a case which we reported, the testes may appear to be enlarged but are actually composed of aberrant adrenal tissue and contain

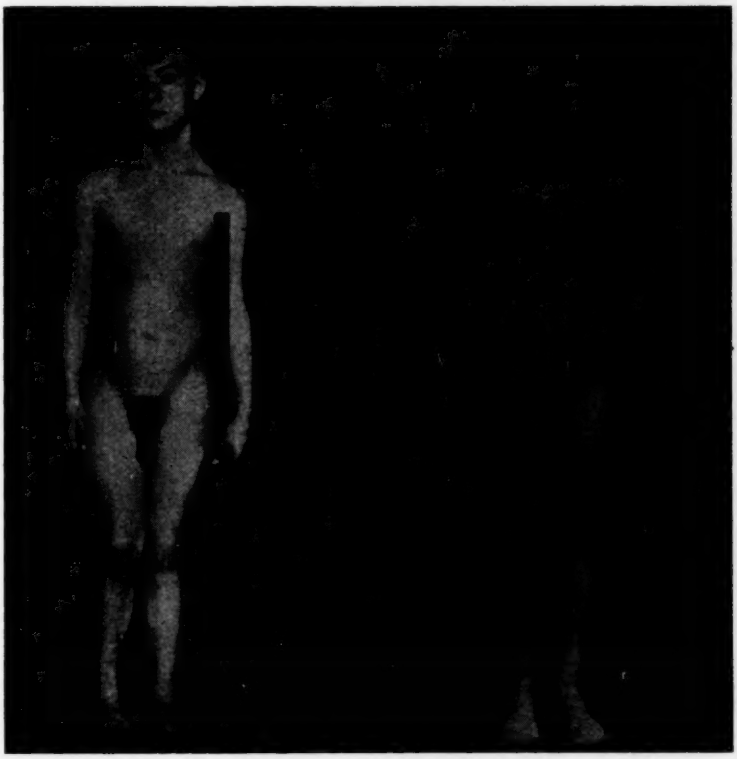

FIG. 5. Types of Male Sexual Precocity. Congenital Adrenal Hyperplasia Contrasted with "Constitutional" Precocity.

Congenital Adrenal Hyperplasia		*Constitutional Sexual Precocity*	
Age:	5 yrs.	Age:	8 yrs.
Height Age:	11½ yrs.	Height Age:	10½ yrs.
Bone Age:	15 yrs.	Bone Age:	11½ yrs.
17-K.S.	45.2 mg./day	17-K.S.	5.4 mg./day
Testes atrophic		Testes adolescent	

no seminiferous tubules. The level of urinary 17-ketosteroids also may be of aid in distinguishing between macrogenitosomia of adrenal origin and precocity due to pituitary or hypothalamic causes. In both conditions the 17-ketosteroids are increased in relation to the patient's age. However, in adrenal hyperplasia the output may greatly exceed the normal adult levels while in other types of precocity they rise only to adolescent or normal adult levels.

The Occurrence of Addisonian-like Symptoms. As mentioned previously, males with congenital adrenal hyperplasia often die in infancy before the excessive sexual development becomes obvious. In the first few weeks of life there may be progressive loss of weight and dehydration, in spite of

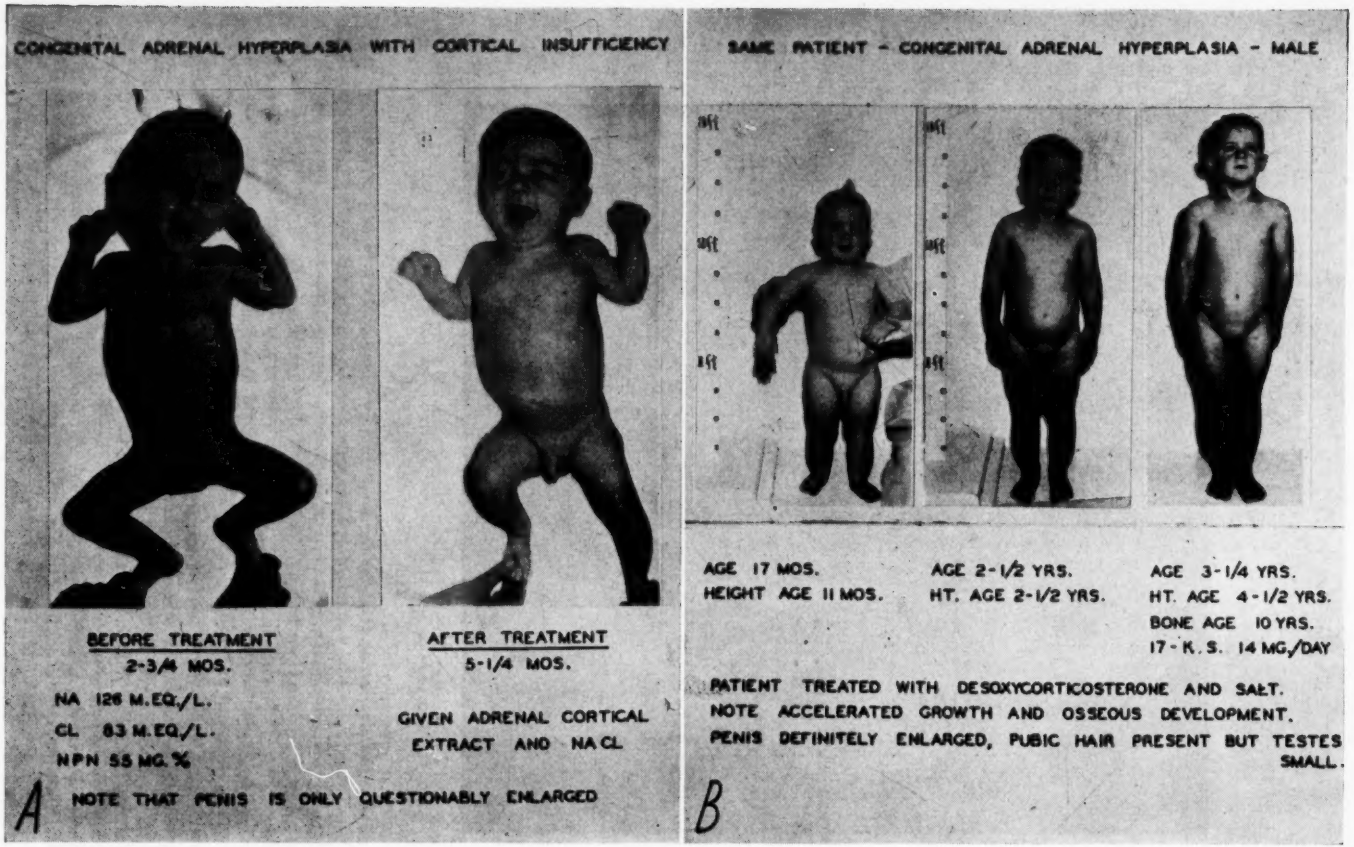
CONGENITAL ADRENAL HYPERPLASIA WITH CORTICAL INSUFFICIENCY
BEFORE TREATMENT
2-3/4 MOS.
NA 126 M.EQ./L.
CL 83 M.EQ./L.
NPN 55 MG.%
AFTER TREATMENT
5-1/4 MOS.
GIVEN ADRENAL CORTICAL EXTRACT AND NA CL
A
NOTE THAT PENIS IS ONLY QUESTIONABLY ENLARGED
SAME PATIENT - CONGENITAL ADRENAL HYPERPLASIA - MALE
AGE 17 MOS.
HEIGHT AGE 11 MOS.
AGE 2-1/2 YRS.
HT. AGE 2-1/2 YRS.
AGE 3-1/4 YRS.
HT. AGE 4-1/2 YRS.
BONE AGE 10 YRS.
17-K.S. 14 MG./DAY
PATIENT TREATED WITH DESOXYCORTICOSTERONE AND SALT.
NOTE ACCELERATED GROWTH AND OSSEOUS DEVELOPMENT.
PENIS DEFINITELY ENLARGED, PUBIC HAIR PRESENT BUT TESTES SMALL.
B

FIG. 6A and B. Infant with Congenital Adrenal Hyperplasia Developing Addisonian-like Symptoms in Infancy Treated with Adrenal Hormones.

an ample intake of fluids and food. The true cause of the dehydration may be masked by the occurrence of vomiting, diarrhea and colic-like symptoms, but the degree is usually greater than would be expected from the gastrointestinal symptoms. The repeated administration of salt solution is usually of only temporary benefit. Some infants die suddenly before much dehydration is evident. In other cases, the patient passes through infancy without mishap and develops Addisonian-like crises in the course of acute infections or other stresses in later childhood. The condition can be diagnosed by finding the serum electrolyte changes characteristic of Addison's disease—low serum Na and high K. If in addition there is a high excretion of 17-ketosteroids, one can be sure that the case is one of congenital adrenal hyperplasia. A patient of Dr. Beach Chenoweth had a serum Na of 90

TABLE IV

DIFFERENTIATION OF TYPES OF MALE SEXUAL PRECOCITY

		Characteristics
Neurogenic	Brain tumor Encephalitis Congenital defects, etc.	Testes mature normally Spermatogenesis may occur Androgen excreted in normal adolescent or adult amounts
Pituitary Idiopathic Activation	"Constitutional type"	
Gonadal	Interstitial cell tumor of testis	Testes usually small and immature Spermatogenesis does not occur Androgen excreted in excessive amounts (In congenital adrenal hyperplasia there may be aberrant adrenal tissue in the testes)
Adrenal	Congenital hyperplasia Tumor	

mEq/l and a serum K of 10.5 mEq/l, while the urinary 17-ketosteroids were 15 mg. per day. When the condition is recognized and properly treated with adrenal cortical extract or with desoxycorticosterone the response is most dramatic. Rehydration and gain in weight occur rapidly as shown in Figure 6A and B.

The occurrence of electrolyte changes and symptoms of adrenal cortical insufficiency with hyperplasia and increased androgenic activity of the gland was first recognized and described by Wilkins, Fleischmann and Howard and by Butler, Ross and Talbot in 1939. Our explanation was that the androgen-producing cells of the adrenal had crowded out or suppressed other cells having salt-regulating and carbohydrate-controlling activities. Recent studies made by Lewis and Wilkins suggest that the explanation is not as simple as this. In the first place, the urinary 11-oxysteroids are not decreased and may be even slightly increased in these cases. Then the administration of adrenocorticotropic hormone (ACTH) to patients with congenital adrenal hyperplasia causes an excessive excretion of sodium, whereas in normal individuals or patients with Cushing's syndrome it causes sodium retention. This suggests that in the cases under consideration the adrenal may secrete a hormone causing excessive excretion of salt rather than its retention.

The Adrenogenital Syndrome in Postnatal Life. Strange to say, cases of adrenogenital syndrome or of Cushing's syndrome which have developed after birth but before the age of 10 years have all been due to neoplasms of the adrenal rather than diffuse hyperplasia of the gland. After the age of puberty both of these syndromes may be caused by either tumor or hyperplasia.

The clinical picture of the adrenogenital syndrome in females beginning after birth is quite different from that caused by congenital adrenal hyperplasia. At birth the genitalia are normally formed, there are a separate vagina and urethra and the clitoris is normal. At a later period, sometimes within the first year of life, there is usually a rapid virilization. The clitoris grows rapidly, acne and pubic hair appear and the voice may become deep. There is accelerated somatic growth, muscular and osseous development. If the onset is after the age of puberty, when female sexual characteristics have developed, there may be cessation of menstruation and atrophy of the breasts. Adrenal neoplasms

may at times be distinguished from hyperplasia by finding a high output of 17-ketosteroids—at times over 100 mg. per day—or a high beta fraction. However, we believe that every case of postnatal virilization merits a surgical exploration of both adrenal glands, as the distinction between neoplasm and hyperplasia cannot be made with certainty. When a tumor is not palpable it can sometimes be localized by pyelograms. Some workers attempt to visualize the adrenal by means of roentgenograms taken after the injection of air into the perirenal spaces. We do not think this risk is warranted inasmuch as surgical exploration is indicated irrespective of the result.

Attention should be called to one condition which may arouse false fears of an adrenal neoplasm. Some girls develop pubic and later axillary hair as early as the age of 5 or 6 years. However, there is no enlargement of the clitoris or evidence of progressive virilization. Neither are there signs of estrogenic activity such as development of the breasts and labia minora nor changes in the vaginal smear which occur ordinarily at puberty. The 17-ketosteroid excretion is usually 2 to 6 mg. per day.

TABLE V

POSSIBLE CAUSE OF SYMPTOMS IN CUSHING'S SYNDROME

Increased Glycogenetic Hormone	Increased Electrolyte-controlling Hormone	Increased Androgen
Diminished N-anabolism Retarded growth Muscular weakness Friability of capillaries and skin Osteoporosis	Hypertension Increased blood volume Serum Na increased Serum K decreased	Hirsutism Acne Decreased ovarian function Increased output of 17-ketosteroids
Diabetic sugar curve Insulin resistance Tendency to obesity		
Increased output of "corticoids" Increased output of 11-oxysteroids		

This condition, which Talbot has called "precocious adrenarche," is probably a constitutional variation in the pattern of puberty caused by a premature elaboration of adrenal androgen occurring before the onset of gonadotropic stimulation of ovarian activity. After a lapse of some years these girls eventually go into normal puberty at about the usual age.

Androgen-producing tumors of the adrenal in males cause macrogenitosomia precox which cannot be distinguished from that due to congenital adrenal hyperplasia. In both conditions the testes remain small and undeveloped and spermatogenesis does not occur. Rapid virilization, especially in later childhood, and a high output of 17-ketosteroids are suggestive of neoplasm. The history of other cases of congenital adrenal hyperplasia in siblings or the occurrence of Addisonian-like symptoms point to congenital hyperplasia.

Feminizing Tumor of the Adrenal. Twelve cases of adrenal tumor causing gynecomastia and more or less testicular atrophy in males have been described. Only one of these cases was in a child, a boy of 5 years. There was a small encapsulated tumor which was successfully removed and which could not be distinguished pathologically from a virilizing tumor. The urinary 17-ketosteroids were 4 mg. per day and a small amount of estrogen was demonstrated in the urine.

Cushing's Syndrome in Children

Pathogenesis. It is generally agreed that the symptoms of Cushing's syndrome are due to excessive production of the hormones of the adrenal cortex. As in other endocrine syndromes, the primary disorder initiating the hypersecretion theoretically might be in the hypothalamus, the pituitary or the "target gland" (i.e., the adrenal). A review of the literature suggests that practically all cases

of Cushing's syndrome beginning before 10 or 11 years are due to adrenal tumor, whereas after this age an adrenal neoplasm frequently is not found.

As discussed previously we have made a somewhat arbitrary distinction between the adrenogenital syndrome and Cushing's syndrome on the basis that in the former the metabolic trend is predominantly toward increased protein anabolism with accelerated growth and muscular development, while in Cushing's syndrome there is increased gluconeogenesis and diminished protein anabolism leading to impaired growth and a tendency to obesity. As a matter of fact, in Cushing's syndrome the different types of adrenal hormones may be increased in varying proportions and this may account for the differences in symptomatology encountered.

Possible Explanation of the Symptoms. Table V offers a tentative explanation for some of the symptoms. Increased secretion of gluconeogenetic hormones causes the amino acids of the metabolic pool to be diverted from protein anabolism toward the formation of carbohydrate. Diminished protein anabolism and tissue repair account for the retardation of growth, poor musculature, fatigability and

TABLE VI

INCIDENCE OF VARIOUS TYPES OF HYPERADRENOCORTICISM IN CHILDHOOD

	Female	Male	Total
Adrenogenital Syndrome (no obesity)			
Congenital Hyperplasia	83	16	99
Postnatal Tumor	29	12	41
Cushing's Syndrome (with or without virilization)			
All under 10 years were due to tumor	22	4	26
Feminizing Tumor		1	1
Total	134	33	167
Hyperplasia	83	16	99
Tumor	51	17	68

the friability of capillaries and skin causing the formation of striae and ecchymoses. Osteoporosis, so common in the spine, is explained by Albright as a failure of repair of the protein matrix of the bones with deficient mineralization secondary to this. The excessive production of carbohydrate accompanied by diminished utilization accounts for the tendency to hyperglycemia and glycosuria and the decreased response to insulin. Obesity may be secondary to the increased formation of carbohydrate, although it is possible that some hormones of the adrenal may have a specific influence on fat metabolism. It is of interest that the fat deposition is greatest on the face and upper part of the trunk causing the so-called "buffalo type" of obesity.

Although the metabolic findings indicate that the effects of the gluconeogenetic hormones predominate over those of androgen, practically all patients with Cushing's syndrome show some evidences of increased androgenic activity. These are manifested by increased growth of sexual hair, seborrhea and acne. There may be some enlargement of the clitoris, although this is usually less marked than in the pure adrenogenital syndrome. The effects of estrogen are suppressed. The output of 17-ketosteroids is increased to varying degrees.

The hypertension and plethora encountered in Cushing's syndrome may perhaps be due to excessive secretion of the electrolyte-controlling hormone, as these symptoms may be produced by the administration of large doses of desoxycorticosterone. A few cases have been reported in which the finding of a high serum Na and Co_2 and a decreased K gave additional evidence that these hormones were in excess.

Incidence of Various Types of Hyperadrenocorticism in Childhood

Table VI shows the incidence of the types of hyperfunction of the adrenal cortex in children, 10 years or younger, which we have been able to collect from the literature and our own experience. Adrenal lesions are four times more frequent in girls than in boys. Congenital adrenal hyperplasia is

the commonest disorder at this period of life. It is remarkable that the cases both of adrenogenital syndrome and of Cushing's syndrome which developed after birth and before the age of 10 years were all due to adrenal tumor. After this age these conditions may be due to either neoplasm or hyperplasia. Of the cases of adrenal tumor developing before the age of 10 years, 41 presented the clinical picture of the adrenogenital syndrome and 26 showed obesity or other evidences of Cushing's syndrome.

Summary

In the adrenogenital syndrome there is increased protein anabolism due to excessive androgen, in Cushing's syndrome inhibition of protein anabolism due to excessive gluconeogenetic hormones. The manifestations of the adrenogenital syndrome differ according to the patient's sex and the age of onset. Congenital adrenal hyperplasia causes pseudohermaphroditism in the female. This can be differentiated from various types of genetic intersexuality by the evidences of excessive androgen from infancy on and by a fairly uniform type of heterosexual development with a persistent urogenital sinus. In the male congenital adrenal hyperplasia causes macrogenitosomia precox which is sometimes accompanied by Addisonian-like symptoms. This can be differentiated from other types of male precocity by the excessive excretion of androgen and lack of maturation of the testes. In postnatal life androgenic adrenal tumors or hyperplasia cause virilization in both sexes unaccompanied by embryonic abnormalities. Occasionally gynecomastia occurs in males. Most of the symptoms of Cushing's syndrome are probably caused by excess of the gluconeogenetic hormones. However, there is also usually an increased secretion of androgen and in some cases evidences of increased electrolyte-controlling hormones.

Discussion

Chairman Jacobsen: You all agree at this point in the program that adrenal physiology is pretty complicated. Now we have some time left and there must be a number of good practical questions that you would like to pose to these experts in adrenal physiology. I would like to ask Dr. Talbot just how he tells whether a sick child is suffering from adrenal cortical insufficiency, and also whether there are any dangers inherent in giving adrenal cortical extract and also desoxycorticosterone.

Dr. Talbot: Dr. Jacobsen has posed three questions. Although they are related, I will attempt to answer them separately.

First: Concerning the diagnosis of adrenal cortical insufficiency, the following may be said. In its pure state adrenal insufficiency results in a variety of symptoms and signs which may be divided into groups according to the following main headings: neuro-muscular, gastro-intestinal, cardio-vascular and miscellaneous. Of the neuro-muscular complaints the commonest manifestations are easy fatigability, weakness, faintness and coma. Less commonly convulsions and dizzy spells may be present. Of the gastro-intestinal complaints the most common are nausea, vomiting, anorexia and weight loss. Less commonly there may be salt craving, abdominal pain and a tendency to constipation. Of the cardiovascular complaints dehydration and microcardia stand out prominently. There also is a moderately marked tendency to hypotension.

Under the miscellaneous heading, skin pigmentation in patients with chronic adrenal insufficiency is a universal finding. There also are certain other abnormalities which may be detected by laboratory tests. These may be divided into two chief groups according to whether they reflect a lack of the adrenal cortical "sugar-fat-nitrogen" hormone on the one hand or the "sodium-potassium" hormone on the other. Under the "S-F-N" heading there is apt to be hypoglycemia. Also for reasons previously discussed, patients with hypoadrenocorticism are much less apt than normal persons to develop ketonuria under conditions of fasting and are less apt to develop eosinophilopenia under conditions of stress.

Under the "Na-K" hormone heading, hypo-adrenal-cortical patients tend to show a lowering in the serum sodium, chloride and bicarbonate concentrations and an elevation in the serum potassium and N.P.N. concentration values.

As previously suggested the foregoing is a brief sketch of the outstanding manifestations of uncomplicated adrenal cortical insufficiency. Consideration of the symptoms and signs listed will reveal that most of them are not specific for adrenal insufficiency, but are changes which may be seen in children suffering from a variety of other diseases. Moreover, it is clear that patients can be suffering not only from hypoadrenocorticism but also from an acute intercurrent infection or other disease.

In addition it is to be remembered that patients may develop adrenal cortical insufficiency very rapidly if the adrenal glands suddenly become destroyed or damaged by a septic, hemorrhagic or other process. For these reasons it often is very difficult to determine whether an acutely sick individual is suffering just from the effects of such a serious condition as overwhelming sepsis or whether he also is lacking in adrenal cortical hormones. As a consequence of these facts most physicians are inclined to assume for the moment that patients with symptoms and signs suggestive of acute adrenal cortical failure have this condition until proved otherwise. This means that they give them therapy appropriate for a patient in "Addisonian crisis."

This leads to a consideration of the second and third parts of the question originally posed, namely, concerning the use of adrenal cortical extract and desoxycorticosterone (DOCA). Adrenal extract is safe to give because very large doses must be administered before untoward reactions develop. A suitable initial dose is about 20 cc. per sq. meter. Subsequently, 3 to 4 cc. per sq. meter per hour may be given. As the patient's condition improves this therapy is reduced gradually. With regard to desoxycorticosterone the situation is quite different. This drug is quite capable of producing serious toxic effects including excess sodium and water retention and marked intracellular potassium depletion. Accordingly, it is recommended that the use of this hormone be avoided except under conditions where it is clearly indicated. Even under such circumstances the dose should be small and in the order of magnitude of 3 to 5 mg. per sq. meter on the first day and 1 to 1.5 mg. per sq. meter on subsequent days.

Chairman Jacobsen: We have quite a number of questions referring to the thymus gland and the lymphatics. I will ask Dr. Talbot to answer those.

Dr. Talbot: The following may be said concerning the thymus gland. In the healthy child this is a relatively good sized structure. If such a child dies suddenly for accidental or other reasons, the gland is seen to be of normal size post mortem. If, on the other hand, a child dies after an illness of more than 1 to 2 days' duration, the gland will appear post mortem to be of much smaller size (so-called acute accidental involution). It now appears probable that the involution is due to an outpouring of the adrenal cortical "S-F-N" hormones in response to the stress of the illness (alarm reaction).

Chairman Jacobsen: Here is a question directed to Dr. Talbot. "What is known of the relationship of the adrenal gland to allergy?"

Dr. Talbot: I wish I knew. I know of no evidence that the eosinophilia seen in allergic patients is a result of adrenal cortical insufficiency. Rather, presently available evidence suggests that there may be two types of eosinophils, one of which is relatively resistant to the "lytic" action of the adrenal hormones. Possibly there is a marked increase in this type of eosinophil in allergic patients.

Chairman Jacobsen: There seems to be a little confusion as to whether the eosinophil count goes up or down in adrenal insufficiency. Will you clear that up?

Dr. Talbot: The eosinophil count is apt to be normal or slightly elevated in patients with adrenal insufficiency. By contrast, the count is apt to be markedly depressed in patients who are producing abnormally large amounts of the adrenal "S-F-N" hormone. As suggested elsewhere such hyperactivity of the adrenal cortices may be seen both in patients with primary adrenal diseases (hyperplasia or cancer) and in endocrinologically normal patients whose adrenals have been stimulated temporarily to increased activity by acute stress of some sort.

Chairman Jacobsen: One more question, Dr. Talbot. Why do babies with congenital hyperplasia of the adrenals vomit?

Dr. Talbot: Infants with congenital hyperplasia of the adrenal glands are apt to have a mixed adrenal cortical syndrome. On the one hand their adrenal glands are producing too much male hormone. On the other they are not producing enough of that adrenal hormone which prevents excess loss of sodium and water and excess retention of potassium. It is the latter disturbance which accounts for the tendency of these patients to vomit. That is, they tend to develop disturbances in water and electrolyte metabolism similar to those seen in patients with ordinary panhypoadrenocorticism. It is guessed that the gastro-intestinal disturbances are due in the final analysis to a derangement in osmotic equilibrium between intestinal contents and body fluids.

Chairman Jacobsen: This one is for Dr. Talbot. Does Dr. Selye claim to have produced rheumatic disease in animals merely by giving DOCA in excess as shown in your lantern slides of the heart?

Dr. Talbot: I don't think that Dr. Selye claims to have produced rheumatic disease by inducing DOCA poisoning. However, I believe he is intrigued by the similarity between the effects produced

and those seen in patients with rheumatic fever. It can be said without question that DOCA poisoning with excess sodium retention and intracellular potassium depletion does produce serious degenerative changes in cardiac musculature. It also produces interesting changes in renal architecture. It is because DOCA is capable of producing such changes that we feel that it should be used very cautiously.

Chairman Jacobsen: We have a number of questions like this.

"Pubic hair in an eight-year-old girl otherwise normal. What is the significance?"

"Does the adrenal govern the excessive hair growth in the fetus?"

"Do children born with heavy sexual hair which is not shed as usual in infancy profit from adrenal therapy?"

Dr. Wilkins, will you answer?

Dr. Wilkins: I am very glad to have the opportunity of saying a word more about sexual hair. One should draw a very sharp distinction between sexual hair and generalized hair growth, hypertrichosis. We see many newborn babies or young children who are covered with hair and look like little monkeys. They have a lot of hair on the back and the shoulders and everywhere else but sexual hair is lacking. That type of hair growth has nothing to do with adrenal or androgen, in my opinion, and is probably merely an abnormality of the hair follicles and hair growth.

The other question is of very great importance, and I meant to mention it in differential diagnosis. What is the significance of pubic hair in an eight-year-old girl, who is otherwise normal?

There is a condition which is important to recognize. We have seen quite a large series of young girls, who at five and six years of age, developed pubic hair and later axillary hair without any evidence of virilization in the enlargement of their clitoris and without much increase in the output of 17-ketosteroids. When one sees such patients at first, the possibilities of an adrenal tumor should be thought of very seriously. These girls develop hair, but do not show progressive virilization. They do not develop breasts or other estrogenic manifestations of puberty. They do not develop enlargement of the clitoris or change in voice or acne. The 17-ketosteroids are only slightly increased, maybe 2-6 a day. Left alone, nothing happens to them. The hair increases on the pubis and in the axillae, but they don't go into puberty until about the average of 10 or 11, and they turn out to be perfectly normal.

These patients have been sent by parents and physicians who were very much alarmed and suspected an adrenal tumor, but the condition is probably merely a constitutional variation in the time that hair appears in response possibly to an early pre-adolescent rise of androgen. The condition is not serious at all and the parents can be reassured, but the patient should be kept under observation from time to time to make sure that virilization does not develop.

Chairman Jacobsen: There are a number of questions asking about the use of adrenal cortical extract in the course of acute infection. Dr. Koepf, will you saw a few words on that?

Dr. Koepf: I do not believe that the routine use of adrenal cortical hormone should be considered in the treatment of infectious diseases of average severity in the adult or child. In the so-called average infection, the alarm reaction (one phase of which is adrenal cortical stimulation) will supply all the additional adrenal cortical hormone needed to combat the infection. The use of large doses of adrenal cortical extract (not desoxycorticosterone acetate) might be helpful, if a patient with a severe infectious disease fails to respond to ordinary therapeutic measures.

Dr. Wilkins: I agree entirely with what Dr. Koepf has said, and what I am saying is not in contradiction.

In contrast to the ordinary infection like pneumonia and so forth, in certain acute infectious diseases—meningitis, diphtheria, overwhelming scarlet fever, and various things—a very acute adrenal failure might occur.

Dr. Horace Hodes at our hospital has studied a large series of these cases (which could be generally grouped as Waterhouse-Friderichsen syndrome) and Dr. Arnold Rich has studied the pathology. The fascicular zone of the adrenal shows very marked degeneration, so it looks like the tubules of the kidneys. The cells are markedly degenerated.

Hodes and the group working with these infectious diseases are very much on the alert to spot these cases of adrenal crisis acute fulminating cases, whether diphtheria, meningitis, or what. These patients go into circulatory collapse with blood pressure dropping, etc. They are hard to differentiate in diphtheria from myocardial failure, but it is important to emphasize to the group of pediatricians the advisability that in this particular group of fulminating acute infections, it is wise perhaps to stand by for emergency adrenal therapy especially in cases of diphtheria where there is a very sudden

acute circulatory collapse without enough myocardial change or between myocardial failure and adrenal collapse other evidence to account for it. I admit that the differentiation is pretty hard, but Dr. Hodes has been able to do it wonderfully well. Perhaps in this condition very intensive and acute therapy with the adrenal cortical extract rather than desoxycorticosterone is indicated.

Chairman Jacobsen: What is the mechanism of increased uric acid production and excretion in rheumatic fever? Dr. Koepf.

Dr. Koepf: The present concept is that the increased uric acid production and excretion is a result of the alarm reaction. Briefly, in acute rheumatic fever tissue cells, under the stress and strain of the disease, utilize more adrenal cortical hormone than under normal conditions. This results in a temporary decrease in the blood level of ACH, and a decrease in the inhibitory action of ACH on the anterior pituitary. Thus, the anterior pituitary secretes greater amounts of adrenocorticotrophic hormone, causing the adrenal cortex in turn to secrete greater amounts of ACH. Along with other steroid hormones secreted by the adrenal cortex, there is an increased production of 11 and 17 oxycorticosterones. This increase in 11 and 17 oxycorticosterones causes protein to be converted to carbohydrate, at a greater-than-normal rate. In the process of this conversion, nitrogen is released and excreted in several forms, one of which is uric acid. If the uric acid excretion does not increase in proportion to the increased production, the serum uric acid levels are elevated.

Chairman Jacobsen: Here is a question for Dr. Koepf.

"Given an experimental animal exposed to low oxygen, 10½%, how soon would you expect a demonstrable change?"

Then a second part: "Why did you wait 24 hours to do determinations?"

Dr. Koepf: In our experiments in which rats were exposed to 10% oxygen, it took 12 hours before we were able to detect increased gluconeogenesis by means of liver glycogen levels although I believe the mechanism of the alarm reaction began as soon as the animals were subjected to anoxia. After twelve hours liver glycogen levels began to rise, indicating increased production of carbohydrate from protein due to increased adrenal cortical hormone secretion.

The reason 24 hours was chosen to do the liver glycogen determinations was because it took 24 hours of anoxia before the increased hormone caused a maximal increase in liver glycogen, and we wanted to use the maximal effect as a measuring stick under different experimental conditions.

Chairman Jacobsen: There are several questions asking about temporary adrenal cortical insufficiency in young infants. Dr. Wilkins, will you speak about those?

Dr. Wilkins: I wish I could give you an authoritative answer on the subject, but I cannot. I might reply by answering one question here that was asked me specially: "Have you seen any cases of temporary adrenal insufficiency in the newborn or in young infants?"

The answer is: No, I have not, except in the cases of congenital adrenal hyperplasia with virilization of which I have spoken. I have looked for them.

The work of Jaudon is a very valuable and important piece of work in calling our attention to the possibility of a temporary adrenal insufficiency in the premature or in young infants. It is something that bears a great deal of thought and considerable investigation. It is a difficult subject, and I am unwilling to admit that it is entirely proven at the present time that all these cases so reported did have real adrenal insufficiency. A great many of the cases Jaudon reported had diarrhea and vomiting and other gastrointestinal symptoms. Certain electrolyte studies were made on some of these, and were strongly suggestive. We have to leave the solution of this question, which is a tricky one—to be solved eventually by very careful and expert work.

I want to warn against over-enthusiasm and blaming adrenal failure for all unsolved problems of dehydration that we see. There may be a tendency in handling prematures or newborn young infants to forget the old knowledge that we have of the many different causes of dehydration in childhood and to start shooting them with the adrenal hormones, without paying sufficient attention to the well founded old methods of treating dehydrating. Although there is a possibility that there may be cases of adrenal failure occurring in young infants who afterward recover and become normal children, we should go very carefully and not allow enthusiasm along that line to blind us to some of the practical sides in handling such children.

Chairman Jacobsen: There are some questions asking about the treatment of pseudohermaphrodism. Dr. Wilkins, you did not mention that.

Dr. Wilkins: This is one of the most difficult and discouraging problems we are faced with at the present time. We are unable at the present time to do anything to combat the excessive androgen

push that these patients suffer and that causes the virilization of the female. It is a most pathetic sight to see these girls gradually become more and more virilized as time goes on.

The problem had been attacked by Dr. Hugh E. Young by the removal of one and a half adrenals. That is not sufficient to do anything. Virilization goes on. The surgical problem seems to be almost hopeless at the present time, although almost complete subtotal adrenalectomies are being done in patients with adrenal hyperplasia causing Cushing's Syndrome, at the Mayo Clinic. The patients afterwards have to be sustained on extensive adrenal hormones with great difficulty and expense. And the results are none too good at the present time.

How should we handle these patients who are female pseudohermaphrodites? If we see them at birth, we are faced with the alternative of whether to raise them as males or females. There may be considerable difference of opinion on this. All I can say is it would be easier to follow at the present time this push of nature, the excessive androgen production that is going to keep up throughout life, and let them become males. Later plastic operations could be done on the hypospadia, with removal of the female organs.

On the other hand, usually the patients are older and have been raised as females before we see them. I am very much opposed to reversing things and turning them into males at that time. So we leave them as females and try to accentuate the female development as much as possible. The clitora should be extirpated. It is a source of embarrassment and erotic stimulation to the children. Later on by plastic surgery a very adequate vagina can be made at the age of puberty, and we can give the patients estrogen and cause a certain amount of breast development. But no matter how much estrogen is given, that will not repress the androgenic effects that are being produced and there will continue to be hirsutism, acne and muscular build.

The only hope at the present time is that perhaps some day someone can find something to have an antagonistic effect upon adrenal androgen, some anti-adrenal drugs, somewhat similar to anti-thyroid drugs.

Chairman Jacobsen: Dr. Wilkins, I want to ask a question about the pseudohermaphrodites.

Let us say that the part of the adrenal cortex which regulates salt and water is not functioning at all, but that there is tremendous hypertrophy of the part producing androgens. Why would it not be well to do a bilateral adrenalectomy on those patients, thereby getting rid of the tumor which is obviously doing harm, and then carry them along with pellet implantation, as you must do anyhow?

Dr. Wilkins: That would be very fine if our replacement therapy was as adequate as you indicate. I have talked recently to Dr. Rynearson and others of the Mayo Clinic who are doing subtotal adrenalectomies for Cushing's syndrome. I won't go into the details of it. I will say they have been driven almost crazy in trying to keep these poor people alive afterwards. A high percentage of them die. Out of their first twelve cases, four developed acute pancreatitis. For a period of about three months, Rynearson tells me, the staff physicians have to sit up day and night with these patients, treating them with hormones, thousands of dollars worth, and salt and sugar and what not. After that time they sometimes come back in better equilibrium and can be maintained on replacement therapy with pellets, but he stated just recently that not one of these is a very normal individual afterward.

Chairman Jacobsen: We have more questions here, but I feel that the alarm reaction or something is setting in here, so we will call it a day. The meeting is dismissed.

Round Table Discussion

THERAPEUTICS OF TUBERCULOSIS IN INFANCY AND CHILDHOOD WITH SPECIAL REFERENCE TO CHEMOTHERAPY

R. CANNON ELEY, M.D., *Chairman, Boston, Mass.*

Chairman Eley: It is advisable to state the proper title of the discussion, should read, "Therapeutics of Tuberculosis in Infancy and Childhood with Special Reference to Chemotherapy." As you will see, this immediately enlarges the field of discussion and does not necessarily limit it to streptomycin.

The U. S. Public Health Service has been conducting a cooperative study on the evaluation of antituberculosis chemotherapeutic agents in juvenile tuberculosis. These studies are being made in several pediatric centers throughout the country and especially in those localities where teaching hospitals are available. Dr. Floyd Feldman of the U. S. Public Health Service is the medical director and coordinator of this huge undertaking. Dr. Ralph Platou is the director of this work at Tulane University, Louisiana, and Dr. William Berenberg has charge of the program at the Childrens Medical Center, Harvard Medical School, Boston.

During the past decade amazing progress has been made, both in the control and treatment of diseases resulting from bacterial invasion. It would naturally follow therefore that these same measures might be applied to the treatment of tuberculosis. The in vitro results obtained by the use of the sulfonamides and their related compounds (i.e., promin, diasone and promizole) suggested their trial in the treatment of tuberculosis in experimental animals. These studies showed that in the hypersensitive guinea pig a deterrent effect on the infection could be demonstrated, but that the infection was not eradicated. When these agents were applied to man, the results were even less favorable as no regression of the disease, quiescence or cure was demonstrated.

Studies have also been made with agents that might prove effective by altering the metabolism of the organism. For example, benzoic and salicylic acids were studied with the possibility that the growth of the organism might be inhibited by interference with its oxidization. None of these substances has as yet proved satisfactory for the treatment of human tuberculosis.

To date streptomycin has been more effective in the treatment of this disease than any other antibiotic agent employed. However, it has its disadvantages as illustrated by (1) the development of resistance of the organism to the agent after its administration over a given period of time, and (2) the appearance of labyrinthine disturbances following prolonged or massive therapy. It is, however, believed that sufficient evidence has been obtained to justify the therapeutic use of streptomycin in certain tuberculous conditions such as: (1) Miliary tuberculosis. (2) Acute tuberculous pneumonia. (3) Tuberculous meningitis. (4) Extra-pulmonary tuberculosis.

Although these encouraging results have been obtained, we should still look upon chemotherapy as an adjuvant to such treatment of tuberculosis as sanatorium care, attention to the nutritional state of the patient and, in certain instances, surgery. These latter are the old and proven measures which still constitute the basic requirements of intelligent therapy.

In view of the results which have been obtained by the use of streptomycin in the treatment of this disease, the urgency and importance of the early diagnosis of juvenile tuberculosis cannot be over-stressed. At the same time every pediatrician appreciates the difficulty this will imply, for only too often the clinical manifestations do not present themselves until the disease has made serious inroads on the patient's health. However, many of these difficulties can be overcome by the routine use of the intradermal tuberculin test. This test can serve as a screening process, selecting those patients who should be carefully observed in the future.

A word of caution is indicated. Since the administration of streptomycin is not without danger of toxic manifestations of a most serious nature, every precaution should be taken to exclude any error in diagnosis.

Dr. William Berenberg, Associate Visiting Physician, Childrens Medical Center, Harvard Medical School, Boston, will discuss the Therapeutic Aspects of Pulmonary Tuberculosis. Dr. Ralph V.

From the Annual Meeting of the American Academy of Pediatrics, Atlantic City, N.J., Nov. 20-21, 1948.

Platou, Professor of Pediatrics, Tulane University, New Orleans, will consider the extra-pulmonary and extra-meningeal types of the disease. Dr. Floyd Feldman, U. S. Public Health Service, will discuss the treatment of tuberculous meningitis, with special reference to the information collected in connection with the cooperative study of the treatment of this disease with streptomycin and other drugs.

Dr. Berenberg. Any attempt to evaluate a new therapeutic procedure for juvenile pulmonary tuberculosis must be examined critically in the light of our accumulated previous experience. In general we have come to look upon childhood pulmonary tuberculosis occurring in the group over the age of 2 to 3 years as a relatively benign disease with a low mortality rate. In this age group it is common to observe widespread exudative reactions heal dramatically in several months. It is obvious that the evaluation of any drug which works over a period of weeks or months will be questionable until large numbers of carefully controlled cases are studied. Under the age of 2 years the mortality rate in pulmonary tuberculosis ranges from 3 to 4% in case finding studies to 30 to 35% in patients admitted to hospitals with frank pulmonary tuberculous symptomatology. In this age group the need for more specific therapy is obvious and any improvement will lend itself to more accurate evaluation.

The chemotherapeutic approach to tuberculous problems has in general been hampered by various limiting factors:

(1) The tuberculous focus is a relatively avascular lesion so that the chemotherapeutic level in the blood locally is usually extremely low. The lesion is classically one of fibrotic proliferation about central areas of destruction. Usually these features combine to result in a situation where the only bacteria available to attack are those at the periphery of the area of reaction.

(2) The well-encapsulated tubercle bacillus itself has proved to be an organism which under ordinary circumstances is extremely hardy and resistant to attack by ordinary bactericidal agents.

(3) The disease is characterized by an insidious, asymptomatic course resulting rarely in sufficient symptoms or signs to allow an early diagnosis. Consequently one detects few early cases which should be most susceptible to therapy.

(4) Streptomycin and most other antituberculous drugs, while having bactericidal properties, act chiefly by virtue of being bacteriostatic. Thus they act chiefly by suppressing the pathologic lesion and allowing nature to heal it. The duration of such a healing process is lengthy and therefore requires a drug which should be non-toxic over a long period of time. Again, because of the required duration of therapy, ample opportunity is allowed for the organisms to become resistant or to permit resistant mutants to flourish.

(5) The final evaluation of chemotherapy is made difficult by spontaneous improvements, variations in individual immunity factors, and the fact that clinical signs and symptoms may be minimal or absent.

In the past year we have treated 12 infants and children with non-miliary pulmonary tuberculosis with streptomycin in doses of 20-40 mg./kg. body weight per day for a period of 90 days. The streptomycin was administered intramuscularly every 12 hours.

(a) Three patients showed improvement beyond that which would have been anticipated under previous types of therapy. Two of these were infants under 2 years of age with widespread exudative spreading infections. The third patient was a 10-year-old boy with bronchogenic spread from an old focus.

(b) Four patients, all between the ages of 2 to 6 years, showed slight or questionable improvement beyond that which would have been anticipated by conservative care.

(c) Five patients, between the ages of 4 to 11 years, with chronic disease and fibrosis were apparently unchanged.

The total number of patients treated to date is too small to permit any conclusions. However, from these few cases and the experience of others reported in the literature, certain features may be described. When clinical symptoms such as cough, sputum, fever and malaise are present, these will ordinarily show improvement within two weeks, and essentially all those who are going to improve will do so within six weeks. Smears, cultures and guinea-pig inoculations of gastric aspirations for tubercle bacilli becomes negative in favorable early cases within 2 weeks in the majority of instances. In old fibrous or caseous lesions, less than 50% become negative and most of these soon become positive again. The presence of resistant organisms offers a real problem in the majority of patients treated beyond 6 to 8 weeks in whom organisms may still be recovered. Serial roentgenograms usually reveal cessation of spread within 1 to 2 weeks. Definite improvement is usually not visualized

before 4 to 8 weeks, but those patients who do improve will continue to do so after therapy has been discontinued.

The available information concerning the use of streptomycin in pulmonary tuberculosis in children is at this date too little to establish any absolute indications for its use and the entire concept of the value of the drug may well change with increased knowledge. However, from the information which is available it would appear that the indications for streptomycin in the treatment of juvenile pulmonary tuberculosis are: (1) Hematogenous miliary disease. (2) Tuberculous pneumonia. (3) Bronchogenic spread. (4) Spreading exudative parenchymal involvement under 3 years of age. (5) Recent rapidly progressive disease not likely to respond to conservative treatment. (6) The development of measles, pertussis or pneumonia in a patient with pulmonary tuberculosis; here the duration of streptomycin therapy need be for only 2 weeks. (7) As a pre- and post-operative measure for tuberculous pulmonary surgery.

No mention of nodal or tracheobronchial disease is included here since this discussion is limited to pure pulmonary problems.

Streptomycin should not be employed in the following situations: (a) Where the prognosis is good with conservative care only. (b) Where the lesion is healing. (c) Where the lesion is minimal, whether detected early or healing slowly. (d) In chronic fibrocaseous disease. (e) In widespread destruction of long standing with cavitation of an adult type.

The chief objections to the use of streptomycin in the above mentioned instances are: (i) It is of little or no value in chronic disease with fibrocaseation. (ii) It is unnecessary in minimal disease and in exudative reactions in children over 3 years, since the prognosis is known to be good in this age group. (iii) The drug is expensive and must be given by intramuscular injection. This usually requires hospitalization which adds to the financial burden and undesirability of the method of therapy. (iv) It may result in the development of resistant strains so that if treatment is subsequently required for more serious complications (e.g. meningitis and miliary tuberculosis) it may be ineffective. The transmission of resistant strains to contacts is rapidly becoming a new and serious hazard in the management of treated tuberculous patients. (v) The toxicity of streptomycin is well established. Little attention need be directed toward local irritation and pain, fever, nausea and vomiting, eosinophilia and agranulocytosis, for they are either rare or can be overcome by withdrawal of the drug. Contact dermatitis in nurses handling streptomycin is not to be regarded lightly. Exfoliative dermatoses in patients have been described and although unusual, they may be fatal. The most common serious toxic effect of streptomycin is vestibular dysfunction of a serious and disturbing nature. The frequency with which this latter complication has been described in patients receiving large doses over a period of time must make us indeed critical of the indications for the use of streptomycin.

Certainly more study will be required, especially as to end results, minimal effective dose, required duration of therapy and associated untoward effects before any final conclusions can be made as to the proper place of this valuable adjunct to the therapy of juvenile pulmonary tuberculosis.

Dr. Platou. Your chairman asked me to concentrate on extrapulmonary and extrameningeal forms of tuberculosis. This leaves for practical discussion based on our own experience and available writings of others only miliary, glandular, osseous, genito-urinary, alimentary and other miscellaneous forms or localizations of the disease! Caution is still the watchword, and for each of these clinical lesions, therapy with streptomycin is still to be considered only adjunctive.

Miliary Tuberculosis

Because of preceding or associated major visceral localizations, it has been difficult to evaluate results of therapy for miliary lesions per se. Striking histologic evidences of healing have been repeatedly noted in many patients at post mortem examination. I found reference to 47 examples of proved acute generalized miliary disease treated with streptomycin in doses of from 1.5 to 3.0 gm. (averaging about 40 mg./kg. for children) daily over periods of from 2 to 10 months and with observations continuing for from 1 to 25 months after treatment was instituted. Slightly more than a third of these were clinically improved (some seemingly arrested), about a third died during therapy, and the others were unimproved or relapsed. These results, expressed even in such crude fashion, are truly remarkable when contrasted with those we were accustomed to expect just a few months ago. We do not yet have adequate information on which to base recommendations as to the best regimes to employ, but most of us feel that various combinations of streptomycin with other

drugs, such as those we are studying at present—promizole and para-aminosalicylic acid, may perhaps lead to better results. The chore of determining the best combinations will be a long and tedious one, but should yield much incidental information of value as we go along.

In most of the early treatment failures, the patients have been classed simply as unimproved. Later failures and clinical relapses have usually been associated with the appearance of meningitis essentially unaffected by continuance of previous therapy. This discouraging complication has led many of us to feel that organisms resistant to streptomycin must be eliminated earlier, before they can multiply or produce new lesions at new sites, by simultaneous administration of other agents, if results are to be further improved.

Pending discovery of the best combinations to employ for improving on the results secured so far, it will behoove all of us to be on the alert for early presumptive evidences of miliary disease among our young patients known to have been infected previously with tubercle bacilli; the importance of routine periodic tuberculin tests thus cannot be overemphasized. Even with our present limited means of therapy, it seems fair to state that the best results will be attained among those patients recognized and treated at the earliest evidences of hematogenous or bronchogenic spread. Results must be in part related to duration of symptoms before treatment, and the resultant load of organisms carried by the patient.

Lymphadenopathy

Apparently excellent results have followed the treatment of acute or chronic tuberculous lymphadenitis, with or without draining sinuses. The usual dose of streptomycin, from 1 to 2 gm., has been given daily. In one of our cases given streptomycin 40 mg./kg. daily for 5 days preliminary to surgical excision of a suppurative draining tuberculous node, uneventful clean healing occurred per primam while administration of the drug was continued for 10 days after the operation. Two other patients in whom nodes were not yet fluctuant have improved rather dramatically with streptomycin alone. Judged by the reports we have been able to find, the best results have been obtained in the most acute cases, but among acute or chronic cases, with or without draining sinuses, the results have been gratifying in more than two-thirds of the patients treated over periods averaging about 4 months. Again, many of these patients with lymphadenitis had extensive tuberculous lesions elsewhere. Certainly the encouraging scattered reports so far published justify additional careful study.

Osseous Lesions

The results for more than 200 patients with proved tuberculous lesions of bones and joints have been reported. Most of these have received 1 or 2 gm. of streptomycin daily over periods averaging about 4 months. Clearing or marked clinical improvement of local lesions has been observed in over half the patients. Roentgenologic evidences of improvement have been noted in about a third of them. Spinal lesions have not responded as well as those in the extremities, and continued improvement after cessation of streptomycin therapy has been noted in many cases. In most patients clinical evidences of local improvement preceded roentgenologic signs of healing by rather long periods. It is impossible yet to define the best time and type of surgical intervention during or after streptomycin therapy, but here again methods will undoubtedly be complementary. The characteristic chronicity of osseous tuberculous lesions and the relatively short time which has yet elapsed since the first cases were treated makes it impossible to formulate any specific recommendations at present, though many fascinating individual case reports furnish valuable suggestions to guide us in our search for the best way.

Genito-urinary Lesions

Judging from the results of 161 adult patients included in 9 different reports, apparent cure or marked improvement has occurred in about 70% of those treated with 1 to 2 gm. of streptomycin daily over periods of from 1 to 8 months, usually about 4 months. We have not yet encountered reports dealing with streptomycin therapy of such lesions in children, and have had no experience with them so far in our own clinics.

Tuberculous Enteritis and Peritonitis

Encountered usually as a complication of advanced pulmonary lesions, little information has been secured as to the effects of treatment for this lesion alone. In one report, clinical improvement was

noted among 10 adults treated, but no definite conclusions could be drawn from this small group. It appears from very meager experience that oral administration is not as effective as the intramuscular method in the treatment of enteritis.

From effects observed among 70 patients with lesions of the alimentary tract included in the recent Veterans Administration report, the authors agreed, "The results are uniformly and remarkably favorable, and tuberculous lesions of the alimentary tract constitute one of the primary indications for streptomycin therapy. This would appear to be another example, already seen in the case of tracheobronchial and laryngeal tuberculosis, of the ease with which lesions of the mucous membrane, as opposed to those of the parenchyma, yield to the attentions of streptomycin."

We ourselves have as yet had no experience in treatment of lesions in the gastrointestinal tract of infants or children; we haven't recognized an example of the condition since streptomycin became available to us.

Miscellaneous Lesions

Scattered and inadequate though occasionally encouraging reports have been encountered on the benefits of streptomycin therapy for tuberculous otitis media, pericarditis and keratitis. None of these permit generalizations, recommendations or conclusions at present. We have under treatment at present an 8-year-old girl who had plenty of evidences of miliary tuberculosis, together with bizarre lesions of skin and muscles, histologically suggestive of dermatomyositis or erythema induratum (tuberculosis indurativum). While response to streptomycin therapy has been gratifying during the first 2 weeks, the skin lesions haven't changed much and the follow-up biopsies haven't yet been repeated.

Dr. Feldman. Any discussion of the prognosis in the treatment of tuberculous meningitis necessitates the consideration of several factors. Most important among these are:

(1) Age of patient. The British Medical Research Council reports fatality rates as follows: Under 3 years of age, 82%; from 3 to 5 years of age, 54%; and from 6 to 8 years of age, 44%. These observations are of course what one might expect, for the earlier in life such an infection occurs, the more vulnerable the patient.

(2) Stage of disease at the time of the introduction of therapy. Early cases of tuberculous meningitis show a fatality rate of 46%, medium cases a rate of 66%, and advanced cases a rate of 86%. It is quite natural that such a conclusion should be drawn, as this is true in most disease processes.

(3) Development of resistant organisms, and

(4) The presence of other active tuberculous foci elsewhere in the body are both detrimental to recovery. The resistance factor is of great importance and statistics from the British Research Council have shown that of 22 patients from whom tubercle bacilli were isolated in the cerebrospinal fluid from the 29th to the 136th day of treatment, 3 became resistant on the 45th, the 87th and 90th days. Twelve of the remaining 19 were still sensitive after 60 days of treatment. These findings are in keeping with those of other investigators who have found the development of resistant strains or variants to be an obstacle.

The method employed in the treatment of tuberculous meningitis, as well as the dosage, has varied with different investigators. These factors must therefore be taken into consideration in the evaluation of the results that have been obtained. When given intramuscularly, the dosage of streptomycin has varied from 0.5 to 3.0 gm./day, given in single or divided doses for periods of from 2 to 6 months. Intrathecally the dose has ranged from 0.025 to 0.100 gm./day for periods of from 4 to 8 weeks. A comparison of the results of the 2 procedures shows a fatality rate of 78% when the intramuscular method alone is employed, as against a fatality rate of 58% when both methods are employed at the time therapy is instituted.

To date the results of such therapy may be summarized as follows: The British Research Council has treated 105 patients; 71% died 7 months after the beginning of treatment, and 27% are reported as in good condition. Debre (Paris, France) has treated 93 patients, 62 of whom died within 14 months. Of the 31 living, 22 are no longer receiving therapy; 12 are normal mentally and neurologically and have received no treatment for a period of over 12 months. (These statistics were obtained from Dr. Noufflard of Debre's Clinic, who attended the discussion.) McDermott (N.Y. City), 9 patients treated; 7 dead within 8 months. Dubois (N.Y. City), 24 patients treated; 5 dead 5 months from the time treatment was begun. Lincoln (N.Y. City),

10 patients treated; 8 living 10 to 20 months from the institution of therapy. In these patients therapy included the use of both streptomycin and promizole. The Veterans Administration (both Army and Navy adult patients) has treated 100 patients from March 1946 to May 1947 with the following results: 49 alive May 1947; 40, October 1947; 24, April 1948. Of the 24 patients, 15 were normal 11 to 25 months from the time treatment was begun. Clinically there have been several types of response to therapy, and these responses might be listed as follows: (a) No response, with rapid deterioration and early death. (b) Slow and progressive deterioration. (c) Short period of improvement followed by slow deterioration. (d) Relapse after a long period of improvement. This relapse may be (i) sudden, or (ii) slow and progressive with ultimate death.

Under the auspices of the Tuberculosis Study Section of the U.S. Public Health Service, a "Cooperative Clinical Study" has been established in order to evaluate different methods of treatment as well as the therapeutic value of the various chemotherapeutic agents. To date 5 investigators have been organized and 33 patients have been studied. Two regimens of treatment have been proposed and alternate cases have been submitted to this plan of therapy. These regimens are as follows:*

1. Streptomycin intramuscularly, 20 mg./kg. body weight every 12 hours for 84 doses.
   Streptomycin intrathecally, 2.0 mg./kg./day for 4 days, then alternate days until at least 4 weeks have elapsed. Continue to 6 weeks if spinal fluid sugar has not returned to normal.
   PAS orally, 0.2 gm./kg./day in 4 doses over a period of 6 months, beginning on 8th day of treatment.
   Promizole orally for 6 months, starting with 0.5 to 1 gm. daily, increasing until blood level is maintained at 2.3 mg./100 cc.
2. Same, but no promizole given.

Although the 33 patients so studied do not constitute a large enough group to permit definite conclusions, yet an examination of the preliminary tables indicates that the patients treated on the two regimens are comparable in respect to age, sex and race. To date there has been no appreciable difference in the results obtained in the two methods of therapy. A study of the survival tables would indicate (1) that most deaths occur during the first few weeks of treatment, and (2) that prognosis is best in the older age groups and in those who are treated early by the combined intramuscular and intrathecal methods.

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* Since this presentation the cooperative study group has decided to increase the dose of streptomycin and to extend the period of therapy.

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SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

EDWARDS A. PARK, M.D., *Editor,* PAUL HARPER, M.D., *Associate*

Statements appearing in this column do not necessarily reflect the opinion of the editors nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

WE ARE publishing two additional letters in the series devoted to the health problems of children of school age. The first is from Mr. John L. Bracken, Superintendent of Schools, Clayton, Missouri, who has been recently elected President of the American Association of School Administrators. Charles C. Wilson, M.D., is Professor of Education and Public Health at Yale University.

The letter from Dr. Caroline A. Chandler is self-explanatory. The editors wish, however, to take this opportunity to note that Dr. Chandler's letter has called attention to an incomplete quotation in their statement as published in the January issue of this column in answer to the letter of Dr. John K. Glen; the resolution which is quoted in the third from the last paragraph of the statement was passed by the Academy in the form given in Dr. Chandler's letter.

February 20, 1949

DEAR DR. HARPER:

It is reported that during the recent war the outstanding features of a number of leading planes were combined to produce a miracle aircraft for military purposes. The idea was commendable, but the resulting plane proved to be useless for all practical purposes.

Judges of female beauty recently designated the fortunate possessors of the world's most glamorous physical features, ranging from Lana Turner's ankles to Jane Russell's commanding, upswept cheekbones. If a single possessor of all these physical attributes could be contrived, she probably would sell apples.

There is no single program of health for school children which can be prescribed for all situations. Such a program would smack of the field of proprietary medicine. The development for child health in each community must be fitted to the community's needs and resources.

Standards are a different matter. Desirable and attainable standards for child health and for means of its development are available. To achieve the objectives posed by these standards becomes the responsibility of each community.

One of the best brief definitions of the purpose of a modern school is "to help children grow up better." The satisfactory health program is a matter of community concern and participation. So are the schools. The children are the most important persons in them. The purposes of the school health program are to support the desirable growth and development of children at every point.

The divisions of school health overlap, but certainly they include health services, health education, the supporting areas of physical education and recreation, and the school environment. The last item is particularly important for, together with the family and the community, it establishes the pervasive climate which influences all of a child's life.

To overestimate the importance of school health services would be difficult. In addition to the service objectives, school health services provide an invaluable focus for health education. Acceptable health services hold to a high standard the safety, the sanitary conditions, and all physical aspects of the schools as they affect children's health. But this is only the beginning.

Health service is most effective in health examinations and follow-through. With parents present at the examination the situation is enhanced. Following a child's development, with complete and readily available records, should bring the school physician, the nurse, the teacher, the psychologist or other helping-teacher, and the parents into a smoothly working combination which will provide health guidance of a high order. Community aspects of school health must be given attention appropriate to local requirements and possibilities.

Most schools have abandoned the race to give each child a physical examination each year. The routine health examination may be scheduled perhaps once in two or three years, with referrals and continuing cases receiving the attention which they deserve.

The criticism most often brought against health education is that it is boresomely repetitious. Children say that facts of structure and function, of nutrition and hygiene are presented to them time after time in almost unchanged form. In some cases this probably is true. But these cases represent dry, factual instruction. The way out is to make health instruction practical; to center it on actual conditions and to interest children in developing health programs. The school physician has an amazing opportunity to vitalize health instruction. He is the outstanding health consultant for every member of the school health council and for every teacher in her concern for the health and instruction of children.

Physical education is not health education, but physical development properly guided supports health. The big-muscle days are pretty well gone. After all, there is small distinction in being the most muscular man in the graveyard! Now the emphasis is on correcting undesirable physical conditions, on providing for stimulating participation in activities and sports, and on developing interests which will survive.

Athletics, an important area of physical education, has strayed too far away into the fields of commercialism and individual or community aggrandizement. The purpose of athletics must lie in sport, school spirit, and enjoyment or it becomes questionable. Athletics is a part of a physical education, and physical education is an integral part of a well-considered program for the development of children and youth. It un-

fortunately has sunk in many instances to the level of a money-making attraction. In our schools we have "thrown away the gate." There is no charge for any game or contest. All costs are paid by the school district, control lodges with the Board of Education, and policies are developed along professional education lines.

Recreation is tied in with the full realization of the objectives which school health claims. In most instances the statement that it is the school's task to help children grow up better is qualified, sharply and immediately. The school program usually is limited to six hours a day, five days a week, and nine or 10 months a year.

Acceptance of full responsibility involves the development of afternoon, evening, and summer programs for children. To be most successful, diversified programs serve the aims of full child development. Often the programs may be developed cooperatively by school and community agencies. The pediatrician can activate public sentiment, can help in the organization, and he is needed in the operation of such a program.

Schools can meet the physical requirements of a healthful situation and still miss the boat. The general environment to which the school contributes so importantly may get out of step. The environment usually distinguishes a school, but it varies from group to group. The spirit of a school is compounded of many things. Type of control, methods of teaching, and relationship with the home are some of them. The spirit is revealed by the respect for children, the understanding of children, and the skill in dealing constructively with children which become evident as school living unfolds. Such items as examinations, report cards, and promotions are important. The extent to which homework impairs the lives of children and others in the homes is only suspected!

Health comes to full flower in a balanced, wholesome, engaging personality. It is to the development of such a personality that the school health program must contribute. Health is the best foundation for a good personality. Understanding of conditions, acceptance of limitations, and adjustment to surroundings often provide an acceptable substitute. Unless the pediatrician sees his place in this development he is unlikely to achieve his greatest service. Unless the school gives the pediatrician full opportunity to make his vital contribution in this total area, it fails to use one of its finest personal instruments. It is good to note that school physicians and members of school staffs are combining their forces for the good of American childhood and youth.

(signed) JOHN L. BRACKEN

February 7, 1949

DEAR DR. HARPER:

I have been interested in the letters appearing under the heading, "The Pediatrician and the Public" and would like to take this opportunity to call attention to the opportunities for pediatricians to make important contributions to school health programs. Interest in school health activities has increased tremendously in recent years, and it is likely that this interest will result in the expansion of present programs and the inauguration of new programs in schools which previously have given little consideration to health. Because of his interest in the influence of such activities on the health of his school-age patients, as well as his interest in all matters affecting the health of children, the pediatrician should become familiar with the health program conducted by the schools of his community. Moreover, the pediatrician and other physicians should be prepared to work cooperatively with Boards of Education and Departments of Health

in planning school health programs and in formulating policies that delineate the scope of school health procedures and relate these to the activities of private practitioners.

Close agreement exists among various professional groups concerning the health role of schools and the importance of school efforts to protect and improve the health of children. A brief statement of school health functions can be presented by grouping such activities into seven categories. Such a statement will form a background for suggesting specific ways in which the pediatrician can help to improve the school health program of his community.

1. A safe, sanitary, and wholesome environment should be provided for school children. Accident hazards must be eliminated and sanitation and housekeeping must attain high standards. Attention must be given to the mental, emotional and social environment of pupils while they are in school, a task that centers attention on the health of teachers, on teaching methods and on such procedures as grade placement in relation to ability, types of report cards and attitudes toward discipline.

2. Pupils should be helped to develop desirable health practices, to understand factors relating to the maintenance of health and prevention of disease, and to develop appropriate attitudes toward health and health practices. The program of health instruction should extend throughout the elementary and secondary school grades and should be adapted to pupil interests and individual and community health needs. At the secondary level it is desirable that a broad, comprehensive health course be offered as part of the program for all pupils.

3. Attention should be given to preventing the spread of communicable diseases at school. Naturally, the school should work closely with the department of health in this and other aspects of their health activities.

4. Each school should have written policies that state how pupils who become injured or sick while at school are to be cared for, and who is to be responsible for providing the recommended care.

5. In every school there should be a program for the periodic appraisal of the health of each pupil through the use of such procedures as: a) teachers' observations, b) screening tests for vision and hearing, c) periodic weighing and measuring, d) health histories, and e) medical examinations. Appraisal procedures provide information which helps teachers to understand their pupils, and identifies pupils who need special attention because of the presence of remediable defects or other health problems. The procedures should be planned to include all aspects of health, physical, mental and emotional.

6. Health appraisal should be followed by a program of health counseling through which pupils and their parents are made aware of the health problems which have been identified and are helped to develop an appropriate program of action directed toward securing needed professional attention. In most instances children will be referred to a private practitioner, but where this is not feasible, referral may be made to outpatient clinics or to other treatment facilities provided by the community.

7. Children with non-remediable defects may require special attention while at school, and in some instances specialized programs of education. Such children include those who are hard-of-hearing or partially-sighted; those who have orthopedic defects or have cardiac damage due to rheumatic fever. Children with speech difficulties should receive speech instruction. In all instances, special programs for handicapped children

should be based on a thorough study of the child's abilities and disabilities, including consideration of the recommendations of the child's physician.

The pediatrician's knowledge of children and of children's health problems can be of great value in the formulation of policies and the development of procedures that will permit schools to carry out effectively and efficiently the various school health functions just described. Ways by which the pediatrician can help may best be illustrated by considering specific problems in several different aspects of the school health program.

In the area of communicable disease control, school procedures sometimes cause parents to believe that treatment to prevent smallpox, diphtheria, tetanus and whooping cough should be delayed until just before the child enters school. The allotment of state funds to local school units may be based on the average number of pupils in attendance each day, a plan which frequently results in children being urged to attain a perfect attendance record even though this requires their presence in school when for their own welfare and the protection of other pupils they should be home. To prevent or correct such situations the pediatrician should work cooperatively with public health officials and school departments and secure their assistance in educating parents to the need for children to be immunized during infancy and to the need for keeping sick children at home regardless of how this affects attendance records. The need for "booster" doses of immunizing substances at the time of entrance to school and the development of regulations concerning the duration of exclusion from school of pupils who have various communicable diseases, or have been exposed to such diseases, are other problems which should be solved by cooperative action of pediatricians, other physicians, the health officer and school officials. Parents should know that these persons have reached agreement concerning recommended procedures.

Numerous questions arise in many communities regarding the program of health appraisal. At what intervals should school medical examinations be provided? What should be the extent of the examination? How can the quality of school medical examinations be improved? What procedures should be used in referring pupils to their physician? Can an examination by a child's own physician be used as a substitute for a school examination? How should the mental and emotional health of children be appraised? Are community resources for the treatment of needy children with health problems adequate?

Viewpoints on many of these questions have been expressed in numerous publications including "Suggested School Health Policies"[1] and "Health Appraisal of School Children."[2] The pediatrician can help interpret recommended policies to school officials and can assist in the development of programs that will benefit children and are also in keeping with the consensus of medical opinion. For example, the report "Suggested School Health Policies" states that "Medical examinations (in schools) should be sufficiently painstaking and comprehensive to command medical respect, sufficiently informative to guide school personnel in the proper counseling of the student, and sufficiently personalized to form a desirable educational experience." School officials need

[1] *Suggested School Health Policies,* Report of the National Committee on School Health Policies, Health Education Council, New York, 1945.

[2] *Health Appraisal of School Children,* Report of the Joint Committee on Health Problems of School Children of the National Education Association and American Medical Association, 1948.

to learn from pediatricians and other physicians the characteristics of a medical examination that will "command medical respect" and they need to know the kind and amount of medical service which is necessary to provide that type of examination. As a guide to the solution of this problem, attention is called to the statement in "Health Appraisal of School Children" that ". . . a minimum of 15-20 minutes of the physician's time (should) be scheduled for the examination of each pupil, including consultation with the pupil or his parents."

Pediatricians can help in the establishment of adequate treatment facilities for needy children. A frequently heard criticism of school health programs is that they provide for the discovery of defects but that nothing is done to see that the conditions are corrected. Where this is the fact, and it usually is not in communities where there is good leadership for school health and public health activities, it may be due to lack of sufficient personnel for effective health counseling or it may be due to lack of appropriate treatment facilities. In the latter instance, the pediatrician may well be one member of a community group which will plan for providing needed facilities. No child should lack the professional health care he needs!

Ways by which the pediatrician can contribute to the school program of health instruction are not so obvious, yet they are numerous and important. Health instruction is primarily a teacher's responsibility. The teacher's instruction encourages pupils to develop desirable health practices, such as selecting an adequate diet, visiting a dentist regularly, brushing the teeth, washing before eating and after going to the toilet, dressing appropriately for weather conditions, attending to lighting and ventilation, etc. Health instruction helps pupils to understand themselves as functioning human organisms and provides information concerning ways to protect and improve personal and community health. Although the teacher develops and conducts health instruction, she frequently can benefit from the advice and assistance of a pediatrician or other persons familiar with the health problems of children. Questions may arise which she cannot answer and concerning which she may seek information. Statements in health texts concerning various health problems may not be clear to the pupils or teacher. The pediatrician can interpret or elaborate on such statements. He may, in fact, be asked to review health texts or audio-visual aids and express an opinion concerning their scientific accuracy. He also may be asked for an opinion concerning the health practices which should be recommended to pupils and the health problems to which attention should be given in the instructional programs. As a specialist in the health of children, the pediatrician can help to guide health instruction along desirable lines.

Schools need the services of a physician in order to conduct an effective modern school health program. As stated in the report of a recent conference,[3] "All schools must have a school physician who will function as a school medical adviser." The medical adviser should work closely with school administrators, teachers and nurses and should advise school authorities on all matters relating to the health of school children. Furthermore, he should act as a liaison between the schools, the health department, voluntary health agencies, and private practitioners. He should assist in formulating school health policies and should advise regarding school sanitation. He should develop programs of health appraisal and health counseling and work with community

[3] *Physicians and Schools,* Report of Conference on the Cooperation of the Physician in the School Health and Physical Education Program, American Medical Association, 1947.

groups to assure the adequacy of treatment facilities for needy children. He should determine the fitness of pupils to engage in various types of physical activities and should help to select pupils who need lip reading, speech correction, or other specialized programs.

Pediatricians, individually or collectively, should concern themselves with the qualifications of persons who are appointed as School Physicians or School Medical Advisers. They may well acquaint individuals or boards responsible for making appointments with the qualifications recommended by the Committee on Professional Education of the American Public Health Association.[4] A well-qualified school medical adviser can facilitate effective cooperation between physicians and schools and can provide the leadership which is needed to assure that school health efforts will fully utilize modern medical knowledge for the benefit of children.

The pediatrician is one of many individuals in the community concerned with the health of children. Through active participation in the development of school health programs he has an opportunity to use his knowledge of children to benefit all children. I hope the time will come when all pediatricians will become thoroughly familiar with the school health programs of their communities and will help schools organize and conduct the best possible types of health programs.

Very truly yours,
(signed) CHARLES C. WILSON, M.D.

February 3, 1949

DEAR DR. PARK:

I should like to call your attention to a statement made in a letter sent out by the Association of American Physicians and Surgeons, Inc. on December 27, 1948 to "all eligible physicians including AAPS members for their information." Under the caption, *A Few AAPS Accomplishments* are listed five items, the third of which reads, "Victory over the American Academy of Pediatrics' proposal to ask for federal aid (with inevitable federal control) for pediatric education and practice."

It is my understanding that following the approval by the Executive Board of the ICH Committee's recommendation for federal support of pediatric education on February 8 and April 30, 1948, the AMA initiated plans to raise funds from private sources for medical education. Because of a willingness to cooperate with the AMA, on June 26, 1948 the ICH Committee recommended that the Executive Board withhold action on seeking federal aid but without "prejudice to justification of federal aid or its need." This recommendation was approved.

At the 1948 Annual Meeting of the Academy in Atlantic City in November, a resolution was passed which stated in part that "*Whereas,* the need for professional leadership of the program to improve medical care is so urgent that assumption of this leadership in the area of improved medical training must not be unduly delayed; therefore, be it *Resolved,* that this Academy is sympathetic with and will support the effort of the American Medical Association to raise the necessary funds for medical education from private sources"; and "that if sufficient private support is not obtained within a reasonable time, then legislation to allocate federal funds for this purpose

[4] Proposed Report on the Educational Qualifications of School Physicians, by the Committee on Professional Education of the American Public Health Association, Am. J. Pub. Health **34**:977, 1944.

should be vigorously supported; provided that such legislation contains specific safeguards to protect the freedom and initiative of physicians and of medical institutions."

To label this willingness on the part of the Academy to cooperate with the AMA as a "Victory over the American Academy of Pediatrics' proposal to ask for federal aid" is not only misleading—it completely disregards the text of the resolution quoted in the preceding paragraph.

Sincerely yours,
(signed) CAROLINE A. CHANDLER, M.D.

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE 81st Congress continues to receive an increasing number and variety of health bills. Among this growing list, we wish at this time to draw attention to the following:

NATIONAL CHILD RESEARCH BILL

In February we published in this column a preliminary draft of "The National Child Research Bill." This bill, with few but significant changes, was introduced into the Senate by Senator Douglas on February 10 as S.904. In preliminary draft form this bill provided for a National Child Research Institute to be established in the Children's Bureau. Thus it was intended that there should be created within the Children's Bureau a separate institute comparable to the National Institutes of Health of the U. S. Public Health Service. In S.904 there is no mention of a separate institute; it is proposed that the Children's Bureau itself be "authorized to establish and carry out a program of research in child life and development" with such additional quarters as may be necessary to enable the Bureau to discharge its functions provided for in this bill. In other respects S.904 is identical to the draft bill previously published.*

THE SCHOOL HEALTH SERVICES BILL

This bill, preliminary draft of which was also published in this column in February, became entangled in legislative strategy from which it has not emerged as of present date (February 23, 1949). In late January there arose within the Senate Committee on Labor and Public Welfare a proposal to add school health services to S.246, a bill calling for $300,000,000 a year in Federal aid to elementary and secondary schools. An additional annual appropriation of $25,000,000 to be used for school health services was suggested as an amendment to S.246 with a formula to be worked out for the distribution of the funds through the state education agencies. (The School Health Services Bill proposed by Senator Saltonstall in the 80th Congress, S.1290, called for an appropriation of $10,000,000 for the first year and $15,000,000 for the second year.)

The Committee rejected the idea of combining the two programs in one bill. It decided that a separate bill should be drafted on the subject of school health services and that the two bills should then be considered together in the light of their interlocking objectives. A subcommittee was named to draft the health measure "expeditiously." Members of this subcommittee are Senators Hill, Douglas, Taft and Smith.

DEPARTMENT OF WELFARE

An Administration bill (H.R. 782) to carry out the President's recommendation

* PEDIATRICS 3:243, 1949.

to convert the present Federal Security Agency into a Cabinet Department of Welfare has now been approved by the House Committee to which it was referred. It is noteworthy that this bill as approved by the Committee creates a "Department of Welfare" instead of a Department of Health, Education and Security. On February 15, the final day of hearings on this bill, Dr. John W. Green of California stated the AMA opinion favoring the creation of a cabinet Department of Health with a physician as secretary and opposing the creation of a department covering education and welfare as well as health. The National Education Association is also opposed to a joint department and has urged a separate agency in the field of education.

It may be anticipated that the Department of Welfare bill will receive prompt action. Federal Security Administrator Ewing has stated that he is wholeheartedly in favor of the bill; the Bureau of the Budget (on behalf of the President) recommends its enactment; former President Hoover testified that he thought "the general consensus of view is that there should be a Department of Welfare."

Local Public Health Units Bill

This bill (S.522), which received favorable attention a year ago in the 80th Congress, was introduced on January 17 by Senator Hill with bipartisan support. It has been sponsored by the National Congress of Parents and Teachers and appears to have high priority among the many health bills. It has been endorsed by the American Medical Association, the State and Territorial Health Officers Association, the American Public Health Association, the National Tuberculosis Association, the National Society for Crippled Children and Adults and other organizations. When introducing this bill, Senator Hill called attention to the great lack of full-time health departments throughout the United States. "This bill" he stated "would take a long step toward helping to get enough trained doctors, nurses and technicians into the local and county health departments to carry on the great fight of preventive medicine. . . . The bill would help provide health examinations for our children at the all-important preschool age when so many physical defects can be discovered and corrected."

In brief the bill would provide Federal grants to states to assist them in establishing and maintaining local public health units in order to provide basic full-time public health services in all areas of a state. Within certain standards to be established by the Surgeon-General, each state would set up its own plan for carrying out the purposes of the bill. The Federal aid thus provided would be in addition to existing grants-in-aid programs such as tuberculosis control, venereal disease control, cancer control, mental health and maternal and child health services. Grants are also provided to enable public and other nonprofit institutions offering training in public health work to train needed personnel for both state and local health work.

It is reasonably certain that this bill will be enacted essentially as it is or will be incorporated into a broader bill along with other measures. Since its enactment would have a close relationship to state action for child health, it is quoted in full below.

S.522

To amend the Public Health Service Act to authorize assistance to States and political subdivisions in the development and maintenance of local public health units, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of

America in Congress assembled, That this Act may be cited as the "Local Public Health Units Act of 1949."

DECLARATION OF POLICY AND PURPOSE

SEC. 2. The Congress hereby finds and declares that—

(a) adequate protection of the Nation's health is essential to the security and well-being of our country and cannot be achieved unless basic public health services are available in every locality through adequately staffed and properly equipped local public health units;

(b) at present more than forty million persons in the United States live in areas not served by local public health units and less than ten million persons live in areas served by units which meet basic minimum public health standards;

(c) many areas cannot support local public health units staffed and equipped to the extent necessary for the provision of the basic public health services essential to the well-being of the community;

(d) it is therefore the policy of the Congress, and the purpose of this Act, in the promotion of the general welfare and in the interest of national security, to assist the States, through the measures provided for in this Act, in developing and maintaining local public health units organized to provide basic full-time public health services in all areas of the Nation and in the training of all types of personnel for local public health unit work.

LOCAL PUBLIC HEALTH UNITS

SEC. 3. (a) Section 315 of the Public Health Service Act, as amended, is amended by redesignating such section as section 304.

(b) Part B of title III of such Act is amended by adding at the end thereof the following new section:

"GRANTS TO STATES FOR LOCAL PUBLIC HEALTH UNITS

"SEC. 315. (a) For the purposes of this section—

"(1) the term 'local public health unit' means the governmental authority of a local area authorized to provide in such area the basic public health services for which funds are made available under this section (including a unit of a State government specifically assigned responsibility for the provision of basic public health services in a local area), or a combination of the governmental authorities of two or more contiguous local areas authorized to provide such services in such combined area;

"(2) the term 'population' (A), as applied to a State, means the population thereof according to the latest estimates available from the Department of Commerce on August 31 of the year preceding the fiscal year (or portion thereof) for which a determination with respect to such population is made under this section, and (B), as applied to less than State-wide areas, means the population of such areas according to the most recent decennial census figures certified by the Department of Commerce that are available on August 31 of the year preceding the fiscal year (or portion thereof) for which a determination with respect to such population is made under this section, increased or decreased in proportion to the increase or decrease since such census of the population of the State as estimated in accordance with clause (A) hereof;

"(3) the average per capita income of the United States or the average per capita

income of a State, as the case may be, means its average per capita income for the three most recent consecutive years for which satisfactory data are available from the Department of Commerce on August 31 of the year preceding the fiscal year for which the determination is made, except that the average per capita income of Hawaii shall be deemed to be equal to that of the continental United States (excluding Alaska) and the average per capita income of Alaska, Puerto Rico, and the Virgin Islands shall be deemed to be equal to one-half of that of the continental United States (excluding Alaska).

"(b) To enable the Surgeon General to assist the States and their subdivisions in establishing and maintaining adequately staffed and equipped local public health units for the provision of basic public health services, there are hereby authorized to be appropriated such sums as may be necessary to carry out the purposes of this section. The sums appropriated pursuant to this section shall be used for making payments to States which have submitted, and had approved by the Surgeon General, State plans for carrying out the purposes of this section.

"(c) Within six months after the enactment of this section, the Surgeon General shall by regulation prescribe—

"(1) criteria for determining the minimum population and financial resources which various types of areas must have, and the minimum number and types of full-time professional and other personnel which local public health units in various types of areas must employ per thousand population, in order to afford reasonable assurance of continued financial support for, and efficient and economical administration of, basic public health services in such areas;

"(2) criteria for determining whether methods for allocating, under State plans, the funds made available under this section to local public health units are equitable and such as to assure the effective use of such funds in the provision of basic public health services;

"(3) subject to the limits set forth in subsection (d) (5), general methods of administration necessary to assure efficient and economical provision of basic public health services under State plans, including the conditions under which compliance with such methods may be postponed;

"(4) types of health services, including the training of personnel for local public health work, which shall be considered basic public health services for which funds may be expended under State plans, consideration being given in such regulations to the types of health services for which Federal aid is available under other provisions of law.

"(d) In order to be approved under this section, a State plan shall—

"(1) set forth a program for the extension of the State plan so as to assure coverage under the plan of all areas in the State;

"(2) contain satisfactory evidence that the State health authority and the local public health units of the State whose populations are covered by the State plan will have authority to carry out the plan in conformity with the provisions of this section and regulations prescribed thereunder;

"(3) provide that each local public health unit providing basic public health services under the plan service an area of sufficient population and financial resources to assure continued financial support for, and efficient and economical administration of such basic health services; and employ full-time personnel of such types and in

such numbers as are required to render minimum basic public health services to the population served by the local public health unit;

"(4) provide for the allocation of all funds received by the State health authority under this section to local public health units participating in the State plan in accordance with methods that will assure equitable distribution and the effective use of such funds in the extension and expansion of basic public health services, and provide that all such funds shall be used by such units solely for the provision of such services;

"(5) provide such methods of administration of the State plan, including methods relating to the establishment and maintenance of personnel standards on a merit basis (except that the Surgeon General shall exercise no authority with respect to the selection, tenure of office, or compensation of any individual employed in accordance with such methods), as may be necessary to assure the efficient and economical provision of basic public health services under the plan;

"(6) provide that the State health authority will make such reports, in such form and containing such information, as the Surgeon General may from time to time reasonably require, and give the Surgeon General upon demand access to the records upon which such information is based. The Surgeon General shall approve any State plan and any modification thereof which complies with the provisions of this subsection and regulations prescribed under subsection (c).

"(e) From the sums appropriated pursuant to this section, each State which has a State plan approved in accordance with subsection (d) shall be entitled to receive for each fiscal year an amount which bears the same ratio to one-third of the expenditures for such year under the plan as the average per capita income of the continental United States (excluding Alaska) bears to the average per capita income of such State, except that (1) in no case may the amount paid to such State for a fiscal year exceed two-thirds of the expenditures under the State plan for such year, and (2) there shall not be counted as expenditures under the State plan for any fiscal year any sum in excess of $1.50 (or such higher amount as may be specified in the appropriation pursuant to this section for such year) multiplied by the population of the local public health units participating in the State plan. If, during the fiscal year, the areas covered by the State plan are changed, appropriate adjustments, prorated in accordance with the time the change becomes effective, shall be made in determining the maximum amount of the expenditures.

"(f) The Surgeon General shall, prior to the beginning of each period for which a payment is to be made, estimate the amount to be paid to the State for such period pursuant to subsection (e), and shall then certify to the Secretary of the Treasury the amount so estimated, increased or decreased, as the case may be, by any sum by which he finds that his estimate for any prior period was greater or less than the amount which should have been paid to the State under subsection (e) for such period. The Secretary of the Treasury shall thereupon, prior to audit or settlement by the General Accounting Office, pay to the State, at the time or times fixed by the Surgeon General, the amount so certified.

"(g) Whenever the Surgeon General, after reasonable notice and opportunity for hearing to the health authority of the State finds—

"(1) that the State plan has been changed so that it no longer complies with the requirements of subsection (d); or

"(2) that in the administration of the plan there is a failure to comply substantially with any provision required by subsection (d) to be included in the plan; the Surgeon General shall notify such State health authority that further payments will not be made to the State from appropriations pursuant to this section (or, in his discretion, that further payments will not be made to the State from such appropriation for activities or areas in which there is such failure) until he finds that the plan again complies with such requirements or until he is satisfied that there will no longer be any such failure. Until he so finds, or is so satisfied, the Surgeon General shall make no further certification for payment to such State from appropriations pursuant to this section, or shall limit payment to activities or areas in which there is no such failure."

GRANTS TO STATES UNDER SECTION 314 OF THE PUBLIC HEALTH SERVICE ACT

SEC. 4. (a) Subsection (c) of section 314 of the Public Health Service Act, as amended, is amended to read as follows:

"(c) To enable the Surgeon General to assist, through grants and as otherwise provided in this section, States, counties, health districts, and other political subdivisions of States in establishing and maintaining adequate public health services, including grants for demonstrations, for the training of personnel for State and local health work, and for the cost to the State health authority of administering the State plan approved under section 315, but excluding grants for basic public health services for which appropriations are authorized under such section, and to enable the Surgeon General to provide demonstrations and to train personnel for State and local health work (directly or through grants to public and other nonprofit institutions offering training in public health work) and to meet the cost of pay, allowances, and traveling expenses of commissioned officers and other personnel of the Service detailed to assist States in carrying out the purposes of this subsection, there is hereby authorized to be appropriated such sums as are necessary to carry out the purposes of this subsection."

(b) The first sentence of subsection (d) of such section 314 is amended to read as follows:

"(d) For each fiscal year, the Surgeon General, with the approval of the Administrator, shall determine the total sum from the appropriation under subsection (a), the appropriation under subsection (b), and the appropriation under subsection (c) which shall be available for allotment among the several States."

(c) Subsection (i) of such section 314 is amended to read as follows:

"(i) All regulations and amendments thereto with respect to grants to States under this section or section 315 shall be made after consultation with a conference of State health authorities and, in the case of regulations or amendments which relate to or in any way affect grants under subsection (c) of this section for work in the field of mental health, the State mental health authorities. Insofar as practicable, the Surgeon General shall obtain the agreement, prior to the issuance of any such regulations or amendments, of the State health authorities and, in the case of regulations or amendments which relate to or in any way affect grants under subsection (c) of this section for work in the field of mental health, the State mental health authorities."

JOSEPH S. WALL, M.D., *Chairman*
Committee on Legislation

NEWS AND ANNOUNCEMENTS

New Aide Named for Health Unit

Dr. Samuel M. Wishik, former assistant director of the Division of Health Services of the Children's Bureau in Washington, has been named head of the New York City Health Department's recently reorganized Bureau for Mothers and Young Children, Dr. Harry S. Mustard, Health Commissioner, has announced. In making the appointment, Dr. Mustard declared that his department's expanded program of services for the protection of premature babies and expectant mothers was "now well under way."

The new Bureau Director is a graduate of Columbia University and the College of Physicians and Surgeons. He did child health work in the Health Department from 1939 to 1942, when he was appointed Senior Assistant Surgeon of the Public Health Service. He was assigned to Hawaii where he served both with the Public Health Service and the Hawaiian Board of Health in charge of maternal and child health.

During the poliomyelitis epidemic there in 1943-44, Dr. Wishik became medical director of the Emergency Poliomyelitis Hospital in Honolulu. As a consultant for the Children's Bureau, and State Department in 1946, he conducted a survey of maternal and child health problems in the Philippines. He is a member of the American Academy of Pediatrics.

* * *

Postgraduate Course in Pediatrics

The Department of Pediatrics, Washington University School of Medicine, St. Louis, Mo., will again offer a postgraduate course in pediatrics for the 1949-50 school year, beginning Sept. 12, 1949. Physicians may take either the first or second months of this course, separate or together, or they may register for the complete nine months' course. Application for information or registration should be addressed to: The Dean, Washington University School of Medicine, St. Louis 10, Mo.

* * *

Friends and co-workers of Dr. John A. Toomey are arranging for a portrait. An artist has been engaged and is already at work. This notice is presented to those who might like to join with the Committee in honoring Dr. Toomey, by contributing to the fund created to meet the costs involved. A photographic copy of the portrait will be sent to each of the contributors to the fund.

Contributions should be sent to Mrs. Marguerite Eisenmann, Secretary, Babies and Childrens Hospital, Room 628, Cleveland 6, Ohio.

* * *

Dr. Eugene Rush, Philadelphia, Pennsylvania, Chief of Pediatrics at Mount Sinai Hospital in Philadelphia, died on February 19, 1949.

* * *

Alumni of the Children's Hospital, Washington, D.C., are invited to a Charter Meeting at the hospital on April 5, 1949 in Washington, D.C. The purpose of the meeting is to formally organize the alumni of the hospital.

* * *

American Board of Pediatrics

Diplomates certified at St. Louis, Mo.—Feb. 18, 19 and 20, 1949.

Austin, Eugene W., M.D., 216 S.E. Riverside Dr., Evansville, Ind.
Beerman, Curtis, A., M.D., 300 Lincoln St., Johnstown, Pa.
Bessire, Milton Carl, M.D., 1052 North 5th St., Abilene, Tex.
Brown, Richard Charles, M.D., 113 E. Williams St., Owosso, Mich.

Browning, Joseph A., M.D., 184 Washington N.E., Warren, Ohio
Choy, Cho, Duke, M.D., 920 East 59th St., Chicago 37, Ill.
Cole, Harold S., M.D., 19 Donaldson Ave., Rutherford, N.J.
Conrad, Clyde Douglas, M.D., Medical College of South Carolina, Charleston, S.C.
Cowart, James T., M.D., Lafayette Office Building, Tampa, Fla.
Estes, Harry M., M.D., 225 Bennie Dillon Bldg., Nashville 3, Tenn.
Feldman, Matthew, M.D., 120 Bogert Rd., River Edge, N.J.
Fischer, Paul M. S., M.D., Pediatric Dept., Univ. Hospital, Ann Arbor, Mich.
Gollub, Samuel W., M.D., 4500 Olive St., St. Louis 8, Mo.
Greenberg, William Burton, M.D., 315 60th St., West New York, N.J.
Hamilton, Caldwell K., M.D., Missouri Theatre Bldg., 634 N. Grand Blvd., St. Louis 3, Mo.
Hoffman, Olga Romanov, M.D., 57 Park Ter. Gardens E, New York 34, N.Y.
Jacob, S. Sprigg, M.D., 401 W. Grand River, East Lansing, Mich.
Kaplan, Max, M.D., 1575 Gilpin St., Denver 6, Colo.
Keeley, Robert Emmett, M.D., 2376 E. 71st St., Chicago, Ill.
Lange, Howard L., M.D., First National Bank Bldg., Belleville, Ill.
Marder, Sidney S., M.D., 116-50 227th St., St. Albans 11, N.Y.
McDonald, Beryl M., M.D., 1102 Broadway, Rockford, Ill.
McDougal, Luther L., Jr., M.D., 705 West Main St., Tupelo, Miss.
Milburn, Conn Lewis, Jr., M.D., School of Med., Western Reserve University, Cleveland, Ohio.
Morrison, James Urban, Jr., M.D., 1430 Tulane Ave., New Orleans, La.
Philipsborn, Herbert F., Jr., M.D., 706 Glencoe Rd., Glencoe, Ill.
Podoll, Elliott, M.D., 2114 Weber Ave., Louisville, Ky.
Roggen, Ivan J., M.D., 716 Malzaan St., Saginaw, Mich.
Severy, Wendell Linwood, M.D., 4614 Sunset Blvd., Los Angeles 27, Calif.
Spinelli, Vincent Arthur, M.D., 27 Ludlow St., Yonkers, N.Y.
Stephens, LeRoy J., M.D., 3284 Ivanhoe St., St. Louis 9, Mo.
Strem, Edward Louis, M.D., 711 Lowry Medical Arts Bldg., St. Paul 2, Minn.
Stull, John D., M.D., 106 North Silver St., Olney, Ill.
Sutton, James Mack, Jr., M.D., 412 Third St., Albany, Ga.
Townsend, Edward H., Jr., M.D., 26 South Goodman St., Rochester, N.Y.
Warner, Robert, M.D., 333 Linwood Ave., Buffalo, N.Y.
Wilkinson, Earle Ewing, M.D., 415 Chesterfield Ave., Nashville, Tenn.
Yamazaki, James N., M.D., Children's Hospital, Cincinnati 29, Ohio

INTERNATIONAL NEWS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

CHILD HEALTH IN BRITAIN

In the last few years there have been great developments in the field of child health. Academic recognition has come relatively late. Before the war there were only four university chairs in the medical faculties, two in Scotland, which were concerned with pediatrics. Three of these were concerned essentially with diseases of children and one, founded in Edinburgh in 1931, was called a chair of "Child Life and Health" giving the emphasis to preventive as well as curative measures. Since 1942, however, many universities have established chairs of "Child Health," each working out in its own way the most satisfactory arrangements in accordance with local conditions. It is thought that it would be of interest to print a series of contributions from holders of the new chairs in England to illustrate the modern developments. The order is purely fortuitous and not necessarily historical.

* * *

BRISTOL UNIVERSITY

Although a Hospital for Sick Children was opened in Bristol in 1857 it was only fifteen years ago that undergraduate teaching commenced therein. This long gap in time is some indication of the delay, which was not uncommon in England, in properly utilising the full available facilities for teaching and research in clinical pediatrics. With the University development since 1906 there has been a gradual extension of interest in the clinical school, and in recent years the surge of activity in Child Health has brought the Children's Hospital into full and proper integration with the other teaching hospitals in Bristol, and now (1948) the hospital is within the officially designated group of the United Bristol Teaching Hospitals. In 1947 the University established a Chair of Child Health and the first professor was appointed in the same year. He has clinical responsibilities in the hospital group and in the neonatal departments of the maternity hospitals and has consultant duties in the clinical area.

There is good liaison between the several children's departments and all clinical material is available for teaching and research. Neonatal and premature baby departments in the large obstetric units at Southmead Hospital and in the Maternity Hospital are in the clinical care of the pediatricians. The Department of Public Health acts in liaison which includes consultant and advisory duties by the Child Health Department and there is an interchange of medical staff between the hospital and the infant welfare clinics. Clinical meetings, Child Health Group discussions, pathology conferences and other occasions for gathering up teachers and students are very satisfactory. General practitioners specially interested in Child Health are encouraged to link up and weekly tutorial class is held for them. In all the teaching, stress is laid upon close integration of preventive and curative aspects and upon the normal infant and child. Special lecture-demonstrations in anatomy are given. The increasing interest of students in all these matters is very encouraging.

There is a close relationship with other departments, e.g., medicine, education, and colloquia are held at frequent intervals.

Postgraduate students are in attendance in order to train for the Diploma in Child Health, or as trainees for consultant duties. Suitable courses for general practitioners are also given.

Undergraduate students are brought in touch with the special considerations of infants and children early in their medical training. In anatomy some emphasis is placed upon the special and comparative features in growth and maturation and the anatomy of the living child is demonstrated. Similarly it is hoped to arrange instruction in some aspects of infant physiology. At later stages in the medical curriculum there is ample scope in the neonatal units, clinical pediatrics, child psychology and psychiatry, infant welfare and all special sections in child health. During their period of clinical training the students spend some of their time in residence. Senior undergraduates attend the hospital on ward rounds, clinical lectures and tutorials. Staff conferences and joint seminars are arranged. At all levels team action is encouraged so that health visitors, mid-

wives, social workers, special schools, probation departments, juvenile courts, children's officers, educationists and others may see the value of their work individually and collectively.

At present there is not a separate examination in Child Health in the qualifying examinations. A separate paper is, however, written and pediatric clinical cases are utilised in the general medical section. The Professor of Child Health is an examiner.

There is integration of function between the departments of Child Health and Preventive Medicine, and the heads of these departments are in frequent consultation concerning their joint interests in the medical school and the child health services of the area.

In Bristol, owing to the great destruction from bombing, departmental accommodation is limited. However, heroic efforts are being expended upon developments, but it will be some years before buildings (virtually a new medical school will be necessary) will be adequate to meet the increasing volume of academic and clinical activity. The background is, however, being formed to provide eventually for the increasing range and numbers of persons and bodies interested in and concerned with child health.

A. V. NEALE, M.D.

BOOK REVIEWS

THE PARATHYROID GLANDS AND METABOLIC BONE DISEASE, Fuller Albright, M.D., and Edward G. Reifenstein, M.D., $8.00, 410 pages, The Williams & Wilkins Company, Baltimore 2, Maryland, 1948.

About 25 years ago Fuller Albright became interested in disorders of the parathyroid glands and other conditions disturbing calcium and phosphorus metabolism. It was in 1925 that the first parathyroid adenoma was removed in Vienna and in 1924 and 1925 that Hanson and Collip independently extracted the active principle of the parathyroid glands. Since this time Albright and a long retinue of coworkers have turned out a large number of classic papers clarifying the understanding of the actions of parathyroid hormone, vitamin D and dihydrotachysterol, the effects of various renal disorders upon phosphorus and calcium, and the nature of bone diseases such as osteitis fibrosa generalisata, osteoporosis, osteomalacia, Paget's disease and polyostatic fibrous dysplasia. The new monograph presents in clear and concise form the accumulation of a quarter century of investigations and gives Albright's views as they stand today.

Albright is never content to merely observe the end results of a disorder but attempts to discover where the primary metabolic disturbance occurs and to trace step by step the sequence of events which follow. He does not hesitate at times to present a bold hypothesis realizing full well that it may be wrong, and then proceeds to test experimentally its validity through clinical investigation. There are those who may disagree with some details of Albright's theories concerning calcium and phosphorus metabolism and bone disorders, but the authors of the monograph have been careful to present and discuss both sides of the argument.

The book is well organized and contains splendid indices and bibliography. Aside from its bearing on the particular subject under discussion, it is to be recommended to the student interested in the methods of clinical investigation of metabolic disorders. In the charts and case studies reported one may see how metabolic balance studies can be planned and executed to answer or at least shed light on the particular question being investigated.

Finally, it is suggested that the student interested in parathyroid disorders read Albright's presidential address delivered at the Association for the Study of Internal Secretions entitled "A Page out of the History of Hyperparathyroidism." (J. Clin. Endocrinol. **8**:637, 1948) as an example of the ability of a scientist to express himself in a delightfully humorous vein.

LAWSON WILKINS

VOLUNTARY MEDICAL CARE INSURANCE IN THE UNITED STATES, Franz Goldman, $3.00, 228 pages, The Columbia University Press, New York 27, 1948.

The author has brought together in this book a great mass of factual data. Medical care insurance is defined as a device for pooling risks and resources against the economic hazards of sickness, injury and maternity. Pooling of risks is feasible only for people able to make regular contributions; even under optimum conditions of employment and income there is a segment of the population who have to depend upon public aid for maintenance and for medical care. There is a larger group of self-supporting individuals and families with many children who can pay only a limited amount toward the full cost of adequate medical care insurance. In periods of depression this group is bound to increase. With these exceptions, the voluntary medical care insurance program meets a real need, as is evidenced by its tremendous growth during the past decade and a half.

Goldman points out that "A medical care insurance plan can be initiated successfully and operated effectively and economically only if it has the willing and intelligent cooperation of all groups concerned. There is need for extensive, intensive and continuous education of the people who are to receive care, the professions and hospitals ready to render service, and the personnel in charge of administration. . . ."

The historical background of such insurance in the United States is presented briefly, and a

chapter is devoted to summarizing the attitude of the American Medical Association, the American Dental Association, the American Hospital Association and other such organizations. Separate chapters are devoted to five types of plans: cash indemnity; Blue Cross, or non-profit hospital service plans; Blue Shield, or non-profit physicians' service plans; group practice plans, and a chapter in which are presented the medical society plans in Oregon, Washington and Hawaii; and plans for low-income farm families. Each of these programs is considered systematically under a variety of headings such as basic principles, history and trends of development, eligibility requirements, types of illness covered, etc.

The student or worker entering this field will find here a great mass of valuable information. The author could have rendered an additional service if he had prepared tables to present some of this information in comparative form. A comparison could be made of such items as scope of services, rate ranges, and the percent of payments which are returned to the payee under these various types of programs. Goldman notes that many of the commercial insurance policies operating on a cash indemnity basis pay less than half the cost of hospitalization, and that a sample study of such a plan showed a "wide margin between the benefits obtained and the actual expenditures made. . . ." Comparable data is not given, but it is generally true that the non-profit or cooperative plans return a much higher percentage of funds to the investor.

The author seems to make a real attempt to present his material impartially so that the reader may make his own decision as to the relative advantage of the different programs discussed. However, this reviewer gains the impression that Dr. Goldman favors compulsory health insurance over the voluntary plans and has other convictions which cannot but influence his presentation. Thus, the author is greatly impressed with the advantages of group practice and gives little space to such problems as the undesirable competition for patients which developed between competing group practice organizations, particularly in some of the western states during the depression years of the 1930s. The reviewer believes that Dr. Goldman has every right to his opinion, but that it would be better if such opinions were frankly stated and the reader could judge accordingly.

This criticism of the author is not intended to minimize the real value of this work. He clearly presents the great contribution of voluntary medical care insurance and recognizes that its potentialities are much greater than its current accomplishments.

The careful student and the specialist in the field will find an excellent bibliographic section.

PAUL HARPER

WE, THE PATIENTS, Sidonie Matsner Gruenberg, $3.50, 303 pages, Harper & Brothers, New York, 1948.

This is a revised edition of a book first published in 1939 and written primarily for parents. It represents, in the author's words, "A point of view that has grown through the years." It deals with a variety of things with which parents are concerned in rearing their children—authority and freedom, punishment, discipline, truthfulness and lying, individual capacities and formation of attitudes. There is a section on the role of the home, school and community in the child's development. The radios, movies and comics are discussed in an unprejudiced manner.

Throughout the book the author reveals a sympathetic understanding of children and their parents. Her "point of view" seems to this reviewer for the most part wise and useful.

One will not find specific answers to individual problems here, but one will find that which is more valuable—a satisfying and practical approach to these problems.

WE, THE PARENTS is recommended for parents, for pediatricians and for all people who work with children. Reading is easy and the ideas are clearly stated.

SALLY ANN PROVENCE